Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/022082

International filing date: 09 July 2004 (09.07.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/486,033
Filing date: 10 July 2003 (10.07.2003)

Date of receipt at the International Bureau: 23 August 2004 (23.08.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

1206730

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APPLICATION NUMBER: *60/486,033*
FILING DATE: *July 10, 2003*

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This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.	CU60285P		

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TITLE OF THE INVENTION (280 characters max)

PHARMACEUTICAL COMPOSITIONS

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	40	**Number of Pages = 58**
☒ Abstract	Number of Pages	1	
☒ Drawings	Number of Sheets	17	☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. **19-2570**	PROVISIONAL FILING FEE AMOUNT ($)	**$160.00**

Respectfully submitted,
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20462

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CU60285P

PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions, and their use in the treatment of gastric reflux.

BACKGROUND OF THE INVENTION

Various treatment for the treatment and/or suppression of gastric acid reflux have included the use of antacids, both liquid and solid as well as the proton pump inhibitors and H_2 antagonists, alone or in combination thereof. Such dosage preparations include compositions containing alginic acid, antacid materials and bicarbonates such as may be found in US 5,888,540; US 5,112,813; US 5,254,591; US 5,036,057; US 4,869,902; US 4,414,198; US 4,613,497; US 4,140,760; WO 01/10405; GB 2 298 365; and GB 2 349 570, whose disclosures are incorporated herein by reference in their entirety.

Prior preparations containing alginic acid or a salt thereof, such as sodium alginate, and a bicarbonate salt, such as sodium bicarbonate, have been known upon chewing in the mouth, to cause the alginic acid to react with the bicarbonate salt, and in the presence of saliva in the buccal cavity, to produce carbon dioxide and a highly viscous solution of, in this instance, sodium alginate. The result of this reaction is a mixture not generally considered acceptable or palatable to the consumer being in the form of a foaming, viscous, sticky mass which has an unpleasant mouthfeel and tends to adhere to the teeth. When the sticky mass is swallowed it then reacts further with gastric acid to form a carbonated raft of alginic acid which floats on the contents of the stomach and thereby suppresses gastric acid reflux. Therefore, there is a need in the art for a palatable, consumer acceptable solid dosage form, including a chewable tablet, of alginic acid and a bicarbonate salt.

SUMMARY OF THE INVENTION:

The present invention is directed to a novel pharmaceutical composition of a chewable tablet which comprises alginic acid or a salt thereof, at least one water soluble carbonate radical precursor present in a proportion sufficient to form a metal alginic acid salt and carbonic acid upon contact with an aqueous solution or gastric fluid; at least one pharmaceutically acceptable calcium salt; and at least one of a first bulk sweetener, or a binding agent wherein the calcium salt, and bulk sweetener or binding agent prior to admixture with the alginic acid are combined together by a wet granulation

process, and wherein the formulation optionally comprises additional excipients such as a second bulk sweetener, talc, mineral oil, and an alkali metal salt of hexametaphosphate, a flavouring agent, an intense sweetener, or a dye.

DESCRIPTION OF THE INVENTION:

The present invention is also directed to preparation of an alginic acid, or a salt thereof containing composition which also comprises an effective amount of an antacid which formulation is both palatable, and acceptable to the consumer, having improved organoleptic qualities. The resulting formulation will, in another embodiment, also provide a longer acting release of the antacid in the stomach.

The pharmaceutical composition, in another embodiment, will also provide and maintain over an extended period of time, the resulting raft/gel in the stomach contents. The composition provides for increased durability of the raft in the stomach contents, and in addition provides for maintenance of a reduced pH in the esophagus cavity. Therefore, another aspect of the present invention is a method of reducing gastric reflux in a mammal in need thereof, comprising administering to said mammal an effective amount of a composition as defined herein.

Another aspect of the invention is a method of reducing the incidence of gastric reflux in the esophageal cavity in a human for a period of time, post ingestion of a meal sufficient to cause gastric reflux in said human for a time period of about 60 to about 480 minutes comprising administering to said human an effective amount of a composition as defined herein. Preferably, the time period is from about 120 to about 300 minutes or longer.

Another aspect of the present invention is a method of maintaining a pH of about 4.0 or higher in the esophageal cavity of a human in need thereof, for a time period of about 120 to about 300 minutes comprising administering to said human an effective amount of a composition as described herein. Preferably, the time period is from about 120 to about 180 minutes or longer. Also, the pH is preferably maintained at a pH of 5.0 or higher for this time period.

Another aspect of the present invention is a method of increasing the duration of a raft, greater than 30 minutes, in the stomach contents of a mammal by preparation of a wet granulate of calcium carbonate with a first bulk sweetner and/or a binding agent prior to admixture with alginic acid, or a salt thereof, and a water soluble carbonate radical precursor, such as sodium or potassium bicarbonate.

Another aspect of the present invetnion is a method of increasing the strength of a of a raft, greater than 30 minutes, in the stomach contents of a mammal by preparation of a wet granulate of calcium carbonate with a first bulk sweetner and/or a binding agent prior to admixture with alginic acid, or a salt thereof, and a water soluble carbonate radical precursor, such as sodium or potassium bicarbonate.

The present invention also provides for a composition which is readily compressible, durable for purposes of packaging and handling, and is disintegrable in a predictable manner such as by chewing, or if necessary by swallowing.

The pharmaceutical composition described herein, may also optionally comprise one or more pharmaceutically acceptable active agents or ingredients distributed within.
A pharmaceutically acceptable active agent as defined herein follows the guidelines from the European Union Guide to Good Manufacturing Practice: Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

The products of this invention are formulated such that a floating raft is formed on top of the gastric contents upon ingestion. In a physiological health disorder commonly referred to as heartburn or GERD (Gastroeosophageal reflux disease), the stomach acid is refluxed in to the esophagus, causing damage to the esophageal lining, hence the sensation of heartburn. A raft formed by the product of the present invention, will form a physical barrier to acid refluxing in to the esophagus, thereby preventing or reducing the continuous damage to the esophageal lining.

The raft is a matrix of alginate salts, the bulk of which is calcium, in co-existence with sodium or potassium ions. It is recognized that additional trace ions, such as magnesium may also be present as an impurity in one or more of the excipients. All of these trace ions may additionally enhance the raft formation, durability and strength thereof. The salt forms are a result of the interaction between the alginic acid and the salt source, such as calcium carbonate, sodium bicarbonate, and/or potassium bicarbonate. The resulting raft is made buoyant by the bicarbonate salt interacting with the stomach acid and generating carbon dioxide gas or bubbles. The bubbles are entrapped in the matrix and thus allow the raft to float on top of the gastric contents (the carbonated gel having a

lower bulk density than the gastric acid). The raft so formed also entraps some of the unreacted calcium carbonate and provides a means for the antacid to continuously neutralise the gastric acid at the interface of the raft and the liquid below the raft. This mechanism provides a long lasting acid neutralization benefit. The calcium ions are believed to serve to cross-link the precipitated alginic acid molecules and thereby strengthen the gel matrix. The raft of this invention has been shown to last upwards of about 5 hours, or more, which otherwise would not possible. In a standard antacid formulation, the antacid component or ingredient neutralizes the acid immediately and does not have an extended neutralization effect. Immediate release antacids provide an acid neutralization benefit lasting upwards of about 40 minutes.

Thus, one of the features of the present invention is that the formulation provides for both an immediate as well as an extended neutralizing acid effect. While the active or therapeutic agent antacid entrapped in the floating raft matrix is providing the antacid effect, in this particular instance, a calcium salt, the resulting entity of the interaction with the stomach contents, i.e., calcium chloride, provides a source of calcium that is absorbed into the mammalians systemic circulation through the gastric mucosa and thereby also provides the health benefits of calcium. The extended release feature of this formulation, where calcium is released gradually over an extended period of time, is ideal for facilitating enhanced absorption of calcium.

In addition, the present invention encompasses the discovery of an improved interaction between the excipients as formulated in this composition and the alginic acid and calcium carbonate, sodium or potassium bicarbonate. This improvement provides for formation of a much stronger raft than would be anticipated, as well as provides for an increased duration of the raft, i.e. a raft which lasts much longer on top of the stomach contents, see Figure 1.

The plots in Figure 1 clearly demonstrate that when all these excipients are used together, the resulting raft provides a long lasting acid neutralization benefit as evidenced by the pH in the raft measuring around 6.5 beyond 200 minutes. When individual excipients are tested one at a time, the raft pH remained at higher levels for a duration ranging from 30 minutes to about 130 minutes. It has further been demonstrated that when these excipients are used in other solid dosage forms the results obtained are very similar to that of tablets.

The interaction discovered here allows one to formulate the solid dosage form with a lower amount of alginic acid per tablet, such as 200mg of alginic acid while unexpectently delivering the performance benefit that outlasts formulations containing 400mg alginic acid per tablet. The

raft pH is maintained at least two to four times longer and the raft strength is about 1.5 to 3 times stronger with formulations of the present invention. The lower, or reduced, use of alginic acid in a solid dosage form formulation, suitable for chewing in the mouth, provides not only considerable cost savings in raw material acquisition costs, but also provides for a more palatable taste and texture for the consumer.

An arbitrary criteria for use herein to assess the pH of the raft is one which should measure up to a pH of about 3.0 or above, and the strength of the raft is to last at least about two hours. However, as the data will demonstrate herein, this is merely a criteria used to understand what excipients produce effects, and is not a limitation on the boundaries or scope of the invention herein.

In the first embodiment of the invention the solid dosage form, such as a chewable tablet, comprises an antacid as the calcium salt, for example calcium carbonate, although any calcium salt meeting the required Food and Drug Administrations monograph for a calcium supplement or an antacid would be acceptable. Many of the pharmaceutically acceptable calcium salts meet these requirements, such as calcium citrate, calcium citrate maleate, calcium maleate, calcium lactate, calcium glyceryl phosphate, or calcium phosphate. The calcium must be adapated for compression into a tablet, and so may be preprocessed by any means suitable, such as slugging, roller compaction, aqueous wet granulation or non-aqueous wet granulation. A wide range of particle size, and grades of such directly compressible calcium are commercially available, and all are acceptable for use herein. To the now compressible calcium salt is added alginic acid, or a salt thereof, sodium or potassium bicarbonate (or a mixture thereof), and at least one excipient which contains one or more hydroxyl groups, such as a starch, a sugar, and/or a polyol, alone or in various combinations thereof. The tablet may also contain as necessary additional pharmaceutical excipients for manufacture of, stability of, disintegration of and customer appeal as necessary. These excipients may include additional sweeteners (conventional sweeteners, such as sucrose, dextrose, maltodextrin, sorbitol, or mannitol; or intense sweeteners, such as aspartame, sucralose, and /or acesulfamine K, etc., alone or in various combinations thereof), lubricants, flavors and colorants. The tablet may suitably be manufactured using conventional tabletting techniques.

Preferably, the calcium is produced as a wet granulate prior to admixture with the remaining excipients. More preferably the calcium carbonate is wet granulated with a first bulk sweetener, and /or a binding agent prior to admixture with the remaining excipients. More preferably, the wet granulate includes both the first bulk sweetener and the binding agent. For purposes herein if the

wet granulate includes both the first bulk sweetener and the binding agent it may be referred to herein as a blend. Preferably, when the blend is a mixture of Calcium Carbonate, Confectionery Sugar, and Corn Starch and includes additional excipients, it is referred to as the master blend. The master blend will also include talc, mineral oil and sodium hexametaphosphate, unless otherwise indicated. In a preferred embodiment, the master blend comprises calcium carbonate in about 40% w/w; starch about 5 %; confectioner's sugar about 50%; talc about 2%; light mineral oil about 1%; and sodium hexametaphosphate at about .4%.

The level of the calcium salt, such as calcium carbonate for use herein, is in the range of about 250 mg to about 1000mg per tablet (free calcium), preferably from about 250mg to 750mg and more preferably about 500mg/tablet.

Suitably for use herein is alginic acid. It is recognized that alginic acid salts such as calcium alginate, or sodium alginate, are also commercially available and may be used herein. One of the most useful properties of these water-soluble alginates is their ability to form viscous solutions at low concentrations. Because of the varied composition of the alginates, different alginates at the same concentration give solutions of differing viscosity. A level of alginic acid for use herein, is in the range of about 140 to about 600mg/tablet, preferably about 200mg /tablet. Experimental data indicates that there is no significant difference of pH profile among 200 mg, 250 mg, 300 mg and 400 mg of alginic acid and also pH profile of 200 mg. alginic acid is more consistent than the other levels of alginic acid.

The water soluble carbonate radical precursor is a metal carbonate, or bicarbonate of an alkali or alkaline earth metal, such as the metals sodium, potassium, calcium, magnesium or manganese, and is present in an amount of about 50mg to about 175mg/tablet, preferably about 140mg per tablet to 175mg, more preferably about 140mg, respectively. Preferably, the water soluble carbonate radical is a salt of bicarbonate, and is sodium or potassium bicarbonate, or a mixture thereof.

The first bulk sweetener and the second bulk sweetener may be the same or different. The sweeteners may be conventional ones such as sugar, confectionery sugar, powdered sugar, sucrose, dextrose, glucose, lactose, or maltodextrin, or may be a polyol such as sorbitol, mannitol, xylitol, maltitol, fructose, polydextrose, or combinations thereof.

Preferably the first bulk sweetener includes, but is not limited to a sugar which is dextrose, sucrose, lactose, confectionery sugar, powdered sugar, or is a polyol which is mannitol, sorbitol, xylitol,

maltitol, maltose and polydextrose, or a mixture thereof. The first bulk sweetener is preferably sugar, mannitol, sucrose, or dextrose, or a combination thereof. More preferably it is confectionery sugar, or powdered sugar.

The first bulk sweetener, if wet granulated with the calcium salt, is present in an amount from about 10% to about 30% of the tablet weight, preferably from about 15% to about 25% by weight

Preferably the second bulk sweetener is confectionery sugar, or powdered sugar, mannitol, sorbitol, sucrose, or dextrose, or a combination thereof. The second bulk sweetener if present, is in an amount from about 10 % to about 50% of the tablet weight, preferably from about 25% to about 40% by weight

The intense sweeteners may include, but not be limited to, aspartame, sucralose, acesulfamine K, and/or saccharin derivatives, or a mixture thereof. The intense sweetener is present in an amount from about 0.02% to about 0.12% of the tablet weight.

If talc is present in the formulation, it is in an amount from 0% to about 1% of the tablet weight.

If mineral oil is present in the formulation it is in an amount from 0% to about 1% of the tablet weight.

Suitable lubricants for use herein include, but are not limited to, magnesium stearate calcium stearate, sodium stearate, Cab-O-Sil, Syloid, stearic acid and talc. If a lubricant is is present in the formulation it is in an amount from 0% to about 3% of the tablet weight.

Suitable binding agents for use herein include, but are not limited to starches, natural gums, and low viscosity cellulosic derivatives.

Suitably if the binding agent is a starch, it is corn starch, modified corn starch, wheat starch, modified wheat starch, Starch 1500, or pregelatinized starch. Preferably the starch is corn starch or modified corn starch. The starch is present in an amount from about 1 % to about 15% of the tablet weight.

Suitably when the binding agent is a low viscosity cellulosic derivative it is a carbomer, hydroxypropylmethylcellullse (HPMC), hydroxypropylcellulose (HPC), MCC,

carboxymethylcellulse (CMC), hydroxyethylcellulose (HEC), or methylcellulose (MC). The cellulosic is present in an amount from about 1 % to about 10% of the tablet weight.

Suitably, when the binding agent is a natural gum it is gum arabic, accacia, carrageenan, guar gum, or tragacanth. The gum is present in an amount from about 0.5 % to about 7 % of the tablet weight.

Alternative binding agents also include povidone (PVP), polaxomer, PEG, or a polymethacrylate. It is recognized that the bulk sweetners may also function as a binding agent, such as maltodextrin, mannitol, sorbital, or polydextrose.

Suitably, if a dye or colourant or a flavorant is present in the formulation it is in conventional amounts.

In a typical tablet according to the invention, the metal carbonate or bicarbonate is used from about 2% to about 8 % by weight of the tablet, and the calcium salt is used from about 10 % to about 50 % by weight of the tablet, the balance being active ingredients and any other formulation expedients desired. The binding agent if present is in an amount from about 1% to about 15%; the first bulk sweetener if present is in an amount from about 10% to about 30% and the second bulk sweetner if present is in an amount from about 10 % to about 40 % by weight of tablet.

A preferred embodiment of the present invention is the following composition:

Ingredient Name	%w/w	mg/tablet or capsule
Master Blend	51.7412	1293.53
Alginic Acid	8.0000	200.00
Potassium Bicarbonate	5.6000	140.00
Mannitol	32.5032	812.58
Calcium Stearate	0.4400	11.00
Intense sweeteners	.0904	2.26
dye	0.1252	3.13
Flavors	1.5000	37. 50
	100.0000	**2500.00**

In one aspect of the invention, the manufacturing of tablets herein involves a) wet granulation of the calcium carbonate; and b) dry blending the wet granulation of calcium carbonate with a first bulk sweeter, such as mannitol, and or a binding agent, such as starch, with alginic acid, potassium or sodium bicarbonate (or a mixture thereof); and optionally adding an intense sweetener, such as acesulfame K, and or sucralose, or a mixture thereof, flavors, a lubricating agent, such as calcium stearate, or magnesium strearate, talc and/or colloidal silicon dioxide; and then c) compressing the resulting blend using a tabletting machine into tablets.

In an alternative embodiment, the manufacturing of tablets herein involves a) wet granulation of the calcium carbonate with at least one of a first bulk sweeter and/or a binding agent; and b) dry blending the wet granulation of step (a) with a first bulk sweeter, if none was used in step (a) or a second bulk sweeter and a binding agent if one was not used in step (a) with alginic acid, potassium or sodium bicarbonate (or a mixture thereof); optionally to this blend may be added an intense sweetener, such as acesulfame K, and or sucralose, flavors, lubricants, such as calcium stearate, or magnesium strearate, talc and/or colloidal silicon dioxide; and then c) compressing the resulting blend using a tabletting machine into tablets.

In a preferred embodiment, the calcium carbonate is wet granulated with both a first bulk sweeter and a binding agent prior to admixing with the alginic acid, and potassium or sodium bicarbonate (or a mixture thereof). Preferably the first bulk sweetener is sugar NF, and the binding agent is corn starch NF. To the granulate is optionally added talc, light mineral oil, and sodium hexametaphosphate. This blend is then, preferably admixed with the alginic acid, the bicarbonate, a second bulk sweetener, such as mannitol, one or more intense sweeteners, flavours and lubricating agents.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

Methodologies

In-vitro testing methodologies were set up in the laboratory based on the methodologies as shown below in order to determine the durablity and strength of the resulting rafts. A measurement of a products performance pursuant to the criteria set forth herein, will produce high quality raft characteristics, such as wherein the pH of raft is about 3.0 or above, and the duration of the raft is at least two hours.

A. Rossett and Rice Tests:

The Rosett and and Rice test is a continuous acid challenge test to model raft behaviour *in vivo*. The neutralization profile of the antacid, raft structure, raft appearance, duration the raft lasts, pH within the raft and pH of the liquid below the raft can be quantitatively and qualitatively measured, as appropriate.

The Rosett and Rice experiment is set up by using a 250ml jacketted beaker connected to a constant temperature water bath equipped with a circulator. The water is circulated through the jacket at 37 C continuously through out the experiment. Two pH probes attached to two pH meters are used to measure the pH in the raft and below the raft. Both pH meters are connected to a computer by serial cables and the installed software collects the data and displays the pH values of both probes.

The contents of the beaker are stirred continuously using a magnetic stirrer at 100 RPM. The antacid sample to be tested is prewetted with 20ml of water inside the jacketted beaker. A fixed volume of acid (100ml) is added to the antacid slurry. Various strengths of acid have been used in the R&R with 0.03N HCl considered the closest approximation of the physiological conditions of the stomach. The pH is monitored as further acid is added at a rate of 2ml per minute. In this test a modification of the original test was used in which reactants are removed via a second pump to mimic gastric emptying. 0.1N HCl is used as the acid in our studies.

Figure 2 demonstrates the set up design.

B. Texture Analysis:

To measure the strength of the raft a commercially available instrument, a Stable Micro Systems TAXT2I Texture Analyser was used. Two types of measurements can be made using this equipment, penetration measurements and pull through measurements. Since, penetration measurements can be made without disturbing the raft prior to measurements, this was the method of choice in the experiments herein. A modified Brookfield viscometer probe was used to measure the strength of the raft.

Texture analysis measurements were made on rafts formed using 0.1N HCl at 37C at 5 min time point.

Experiment 1

Sodium and Potassium Bicarbonates

The effects of Sodium and Potassium Bicarbonates on the resulting raft at various levels has been evaluated within the context of the present invention.

Two types of bicarbonates were selected as the best excipients to aide in development of the raft, sodium bicarbonate and potassium bicarbonate. Potassium Bicarbonate is preferred as there are health benefits associated with potassium usage in contrast to sodium.

The Rossett & Rice and Texture Analyzer testing was used to evaluate various levels and reduce taste issues without compromising the raft formation, its lasting ability, and its strength. The table below outlines the level differences of the bicarbonates tested. In order not to introduce other variables into the formula the calcium salt, Calcium Carbonate was held constant at a level of 500mg, and the Alginic Acid was held at a level of 300mg. The tests were performed at a two-tablet /per dose level.

TABLE 1

BICARBONATE SAMPLES

Ingredient	Level Bicarbonate/ t	Results Reference
Sodium Bicarbonate	140 mg	Graph F, and Table 2
Potassium Bicarbonate	140 mg	Graph C, and Table 2
Sodium Bicarbonate	100 mg	Graph D, and Table 2
Potassium Bicarbonate	100 mg	N/A*
Sodium Bicarbonate	70 mg	Graph E, and Table 2
Potassium Bicarbonate	70 mg	N/A*
Sodium Bicarbonate/Potassium Bicarbonate	70/70 mg	Graph G, and Table 2

* Results at 140mg of Sodium vs. Potassium Bicarbonate provided similar data, therefore these samples are not shown herein, or were not tested.

B. Texture Analysis of samples were performed at a two-tablet dose. The samples in Table 2 are the average of two runs performed on the same experiment.

Table 2

TEXTURE ANALYSIS RESULTS

Bicarbonate & Level		Average Force (g.)
Sodium Bicarbonate	140 mg	5.451
Potassium Bicarbonate	140 mg	16.706
Sodium Bicarbonate	100 mg	N/A*
Sodium Bicarbonate	70 mg	N/A*
Sodium / Potassium Bicarbonate	70 mg/ 70 mg	10.719

* Samples were not tested due to poor Rossett & Rice results, reference Graphs D and E.

Conclusion:

Samples for Sodium Bicarbonate at levels of 140, 100, and 70 mg per tablet were tested. The Sodium Bicarbonate at the level of 140 mg. per tablet provides acceptable raft results lasting for 130 minutes, while maintaining a pH between 5.5 and 6.0. Sodium Bicarbonate at 100 mg. per tablet provided raft results lasting for 60 minutes, while maintaining a pH between a range of 6.5 and 4.0. The 70 mg. per tablet sample provided results for pH between a range of 6.5 and 3.0 for approximately 100 minutes. Both the 100 and 70 mg. per tablet were inconsistent through out the Rosette and Rice testing. It was determined that the 100 and 70 mg. amounts as compared to the 140 mg fall short of the 2 hour time point chosen herein, with a pH above 3.0 for the better product performance, and herefore the 140 mg per tablet level for Sodium Bicarbonate was determined to be a more optimal level for use herein.

Rossett and Rice tested on at a level of 140 mg. per tablet of Potassium Bicarbonate (Graph C*) and Sodium Bicarbonate (Graph F) provided consistent results of raft lasting for 130 minutes, while maintaining a pH between 5.5 and 6.0. The texture Analysis of these samples shows that the Potassium, with an average force (g.) of 16.706, provides a stronger raft structure than the Sodium, with an average force (g.) of 5.451. Based on this data from both of these excipients Potassium Bicarbonate at a level of 140 mg. per tablet provides a stronger and long lasting raft (*note unusual dips in pH during testing are believed due to raft thickness reducing by the carbonate bubbles popping during the test).

In efforts to reduce negative taste effects of the Potassium Bicarbonate, both Potassium and Sodium were tested in combination at 70 mg. per tablet equaling 140 mg total. The Rossett

and Rice testing (Graph G) provided raft results lasting for approximately 90 minutes, while maintaining a pH between a range of 6.5 and 3.5. However, as compared to Potassium Bicarbonate at 140 mg. per tablet level this combination does not meeting the 2 hour with a pH above 3.0 suggested requirement for improved product performance, therefore making the 140 mg per tablet of either the Sodium or Potassium the better choice.

It should be noted that the Rossett & Rice test, generally calls for 10 ml. of water to be added to the powder sample to form slurry. It was discovered that 10 ml. was not sufficient enough to wet the powder. A test sample was run following the method with the use of 20 ml. to form the slurry. Results of the test sample using 20 ml. compared to 10 ml showed a significantly better raft formation.

Experiment 2

Bulk Sweetener

In an effort to incorporate a bulk sweetener into the formulation, Rossett & Rice and Texture Analyzer testing was used to evaluate various representative sweeteners without compromising the raft characteristics and additionally improve the texture and test of the finished product.

The commonly used bulk sweeteners Dextrose, Sorbitol and Mannitol were selected for initial evaluation. Dextrose was performed at three different levels whereas Sorbitol and Mannitol were performed at only one level. The sweeteners were tested with the level of 400 mg Alginic Acid per tablet, except Sorbitol. Sorbitol was tested with the level of 300 mg and 400 mg per tablet. 20 ml. of water was added to powder to form slurry for all of these experiments.

Rossett & Rice test and Texture analyzer test were performed for following experiments with one run for the Dextrose experiment and two runs for Sorbitol and Mannitol experiments, at a two-tablet dose level. The blend to which the second bulk sweetener was added consists of:

500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid +674 mg Confectioner's Sugar + 71.43 mg Corn Starch + 9.1 mg Sodium Hexametaphosphate. For purposes of this experiment this is referred to as the Master Blend.

a) Master Blend + Alginic acid 400mg + Sodium Bicarbonate 140mg + Dextrose 125 mg

b) Master Blend + Alginic acid 400mg + Sodium Bicarbonate 140mg + Dextrose 250 mg
c) Master Blend + Alginic acid 400mg + Sodium Bicarbonate 140mg + Dextrose 500 mg
d) Master Blend + Alginic acid 400mg + Sodium Bicarbonate 140mg + Sorbitol 500 mg
e) Master Blend + Alginic acid 300mg + Sodium Bicarbonate 140mg + Sorbitol 500 mg
f) Master Blend + Alginic acid 400mg + Sodium Bicarbonate 140mg + Mannitol 500 mg

The experiment of Sorbitol 500 mg with 400 mg Alginic Acid and 140 mg Sodium Bicarbonate produced a strong raft. The solution below the raft had no floating particles compared to other experiments. The pH of the raft for Run #1 and Run #2 was measured above 5.5 until about 120 minutes. (See ***Figure 8***)

The experiment of Sorbitol 500 mg with 300 mg Alginic Acid and 140 mg Sodium Bicarbonate also produced a strong raft. The same observation like Sorbitol with 400 mg Alginic Acid was made for this experiment which was the solution below the raft had no floating particles compare to other experiments. The pH of the raft for Run #1 and Run #2 was measured above 6.0 until about 140 minutes. (See ***Figure 9***)

The experiment of Mannitol 500 mg with 400 mg Alginic Acid and 140 mg Sodium Bicarbonate also produced a strong raft. The pH of the raft for Run #1 and Run #2 was measured around 5.0 for about 100 minutes and 140 minutes, respectively. The unusual ups and downs in the raft pH are due to the raft thickness reducing by the bicarbonate bubbles popping during the test. (See ***Figure 10***)

Various samples featured in Table 1 were tested to determine the strength of the raft formed. The texture analysis of these samples shows that the Mannitol, with an average force (g.) of 12.332, provides a stronger raft structure than Sorbitol, with an average force (g.) of 9.862 and 6.629. The dextrose was not tested due to poor performance when conducting the Rossette and Rice testing.

Based on the Rosette & Rice and Texture Analysis data for both Mannitol and Sorbitol, either of the two raw materials are preferable for use a bulk sweetener. Sorbitol and Mannitol at a level of 500 mg. per tablet produces a strong and long lasting raft, additionally sorbitol is more cost efficient than mannitol.

Texture Analysis of samples in ***Table 3*** below is the average of two runs performed on the same experiment.

Table 3

TEXTURE ANALYSIS RESULTS

Bulk Sweeteners	Average Force (g.)
Dextrose 125 mg + Alginic Acid 400 mg	N/A*
Dextrose 250 mg + Alginic Acid 400 mg	N/A*
Dextrose 500 mg + Alginic Acid 400 mg	N/A*
Sorbitol 500 mg + Alginic Acid 400 mg	9.862
Sorbitol 500 mg + Alginic Acid 300 mg	6.629
Mannitol 500 mg + Alginic Acid 400 mg	12.332

* These samples were not performed due to the poor performance when conducting the Rossette and Rice testing.

Experiment 3

Components of Master Blend (MB)

Various component(s) of the MB have been separately tested in order to determine their role in the formation of strong raft in the presence of Alginic acid and Sodium Bicarbonate.

From previous experiments, it was decided to use 300 mg Alginic Acid per tablet and 140 mg Sodium Bicarbonate per tablet for all the experiments in this section.
20 ml. of water was added to powder to form slurry for all the experiments.
Rossett & Rice test and Texture analyzer test were performed for following experiments to meet the above objective. Two runs of each experiment, at a two-tablet dose, were performed for both Rossett & Rice and Texture analyzer.

a) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid

b) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid + 71.43 mg Corn Starch

c) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid +674 mg Confectioner's Sugar

d) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid + 27.86 mg Talc

e) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid + 4.55 mg Sodium Hexametaphosphate

f) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid +674 mg Confectioner's Sugar + 71.43 mg Corn Starch

g) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid +674 mg Confectioner's Sugar + 71.43 mg Corn Starch + 4.55 mg Sodium Hexametaphosphate

h) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid +674 mg Confectioner's Sugar + 71.43 mg Corn Starch + 4.55 mg Sodium Hexametaphosphate in solution

i) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid +674 mg Confectioner's Sugar + 71.43 mg Corn Starch + 9.1 mg Sodium Hexametaphosphate

j) 500 mg Calcium Carbonate + 140 mg Sodium Bicarbonate + 300 mg Alginic Acid +674 mg Confectioner's Sugar + 71.43 mg Corn Starch + 9.1 mg Sodium Hexametaphosphate in solution

Texture Analysis of samples in ***Table 4*** is the average of two runs performed on the same experiment. **Note:** 300 mg Alginic Acid and 140 mg Sodium Bicarbonate were used in each run along with different components of Master Blend.

Table 4

TEXTURE ANALYSIS RESULTS

Components	**Average Force (g.)**
Calcium Carbonate (alone)	*4.271*
Calcium Carbonate + Corn Starch	*4.011*
Calcium Carbonate + Confectioner's Sugar	*3.499*
Calcium Carbonate + Talc	*5.529*
Calcium Carbonate + 4.55 mg Sodium Hexametaphosphate	*5.336*
Calcium Carbonate + Confectioner's Sugar+Corn Starch	*3.798*

Calcium Carbonate + Confectioner's Sugar+Corn Starch +4.55 mg Sodium Hexametaphosphate	*4.711*
Calcium Carbonate + Confectioner's Sugar+Corn Starch +9.1 mg Sodium Hexametaphosphate	*3.653*
Calcium Carbonate + Confectioner's Sugar+Corn Starch +13.65 mg Sodium Hexametaphosphate	*4.017*

Conclusion:

Calcium Carbonate in presence of Alginic Acid and Sodium Bicarbonate did not form strong raft. The raft was observed broken in few pieces. The pH of raft was dropped below 3.0 within 15 to 30 minutes of run time.

Corn Starch in mixture with Calcium Carbonate and in presence of Alginic Acid and Sodium Bicarbonate did not help in forming strong raft. Loose particles were visible below the raft (in solution). The pH of raft was dropped below 3.0 within 15 to 30 minutes of run time.

Confectionery Sugar in mixture with Calcium Carbonate and in presence of Alginic Acid and Sodium Bicarbonate formed a weak raft. The pH of raft in Run #2 was dropped to 3.0 and below after about 65 minutes of run time where as in Run #2 the pH dropped to 3.0 and below after about 45 minutes of run time. A problem developed in Run #1 because of loose particles in solution. The Hydrochloric Acid replacing tube was clogged, and was not pumping out Hydrochloric Acid from the jacketed beaker. This was resulted in decreasing the pH of solution below the raft because the second tube was still pumping Hydrochloric Acid to the jacketed beaker. The pH of both raft and solution below the raft was measured around 5.0 from the beginning of the run.

Talc in combination with Calcium Carbonate and in presence of Alginic Acid and Sodium Bicarbonate did not produce strong raft. The pH of the raft was below 3.0 after about 26 minutes.

Sodium Hexametaphosphate and Calcium Carbonate in presence of Alginic Acid and Sodium Bicarbonate did not produce strong raft. The pH of raft, in Run #1 and Run #2, was dropped below 3.0 after about 18 minutes and 55 minutes, respectively.

The mixture of Calcium Carbonate, Confectionery Sugar and Corn Starch in presence of Alginic Acid and Sodium Bicarbonate produced a thin and weak raft. The pH of the raft measured above 3.0 for 25 to 30 minutes.

The mixture of Calcium Carbonate, Confectionery Sugar, Sodium Hexametaphosphate (4.55 mg/tablet) and Corn Starch in presence of Alginic Acid and Sodium Bicarbonate produced a strong raft. The solution below the raft had much less particles floating as compared to other experiments. The pH of the raft for Run #1 and Run #2 was dropped to below 3.0 after about 90 minutes and 140 minutes, respectively.

The mixture of Calcium Carbonate, Confectionery Sugar, Corn Starch, and Sodium Hexametaphosphate (4.55 mg/tablet) in solution with presence of Alginic Acid and Sodium Bicarbonate produced a reasonably strong raft. The pH of the raft for Run #1 and Run #2 was dropped to below 3.0 after about 130 minutes and 120 minutes, respectively.

The mixture of Calcium Carbonate, Confectionery Sugar, Sodium Hexametaphosphate (9.1 mg/tablet) and Corn Starch in presence of Alginic Acid and Sodium Bicarbonate produced a raft like a gel or sponge. The pH of the raft, in Run #1 dropped below 3.0 after about 186 minutes while in Run #2 after about 90 minutes.

In brief, the mixture of Calcium Carbonate, Confectionery Sugar, Sodium Hexametaphosphate (4.55 mg/tablet) and Corn Starch in presence of Alginic Acid and Sodium Bicarbonate produced a long lasting raft. Moreover, the double amount (9.1 mg/tablet) of Sodium Hexametaphosphate did not add any additional advantage for the formation of strong raft. Furthermore, adding Sodium Hexametaphosphate in powder form, or in solution, did not create any effect in the formation of raft. Therefor, it can be added in either form during the processing.

For the texture analysis, various samples were tested to determine the strength of the raft formed. The texture analysis of these samples shows that the mixture of Calcium Carbonate and Talc, with an average force (g.) of 5.529, the mixture of Calcium Carbonate and Sodium Hexamethaphosphate, with an average force (g) of 5.336 and the mixture of Calcium Carbonate, Confectioner's Sugar, Corn Starch, 4.55 mg Sodium Hexametaphosphate, with an average force (g) of 4.711 provides a better texture than other samples.

Based on the Rosette & Rice and Texture Analysis data, it was concluded that all the raw materials (Calcium Carbonate, Confectioner's Sugar, Corn Starch, 4.55 mg Sodium Hexametaphosphate) together form a strong raft as well as provide good texture.

Experiment 4

Formation of a Raft with a Dry Blend of CaCO3

In order to determine the effects of a dry blend of calcium carbonate the ingredients in the table below were all weighed out individually. They were combined in a jar and mixed thoroughly by tumbling the glass jar. To remove clumps, the blend was passed through #20 sieve mesh screen

Formula 1: Dry Blend with CaCO3

Ingredient	mg/tab
Calcium Carbonate	500mg/tab
Alginic Acid F120 NM	200mg/tab
Potassium Bicarbonate	140mg/tab
Mannitol 200 SD	809.48 mg/tab
Calcium Stearate NF	11 mg/tab
Acesulfame K	1.12mg/tab
Sucralose, NF	1.12 mg/tab
Flavours	27.4mg/tab

In a similar manner a formulation of a Dry Blend without CaCO3 was produced, having the following formula:

Formula 2: Dry Blend without CaCO3

Ingredient	mg/tab
Alginic Acid F120 NM	200mg/tab
Potassium Bicarbonate	140mg/tab
Mannitol 200 SD	809.48 mg/tab
Calcium Stearate NF	11 mg/tab
Acesulfame K	1.12mg/tab
Sucralose, NF	1.12 mg/tab
Flavours	27.4mg/tab

Formation of Granulated Blends

The components were combined in respective jars labelled A-I;

Distilled water was added to each jar to prepare granulated materials for testing;

The granulations were dried overnight, then ground with a mortar and pestle.

Table 5

Formation of Granulated Blends

	Excipients	mg/tab.	Theoretical	Actual Wt.(g)
			Wt.(g)/20 tab.	/20 tab.
A	Calcium Carbonate	500.00	10.0000	10.0471
	Starch(Corn)	71.43	1.4286	1.4224
B	Calcium Carbonate	500.00	10.0000	10.0259
	Sugar, Powder	654.79	13.0958	13.097
C	Calcium Carbonate	500.00	10.0000	10.0023
	Talc	27.68	0.5536	0.5534
D	Calcium Carbonate	500.00	10.0000	10.0091
	Light Mineral Oil	15.08	0.3016	0.3015
E	Calcium Carbonate	500.00	10.0000	10.0471
	Sod.Hexa Metaphosphate	4.55	0.091	0.0913
F	Calcium Carbonate	500.00	10.0000	10.0163
	Starch(Corn)	71.43	1.4286	1.4269
	Sugar, Powder	654.79	13.0958	13.0905
G	Calcium Carbonate	500.00	10.0000	10.003
	Starch(Corn)	71.43	1.4286	1.4268
	Sugar, Powder	654.79	13.0958	13.0931
	Talc	27.68	0.5536	0.555
H	Calcium Carbonate	500.00	10.0000	10
	Starch(Corn)	71.43	1.4286	1.4262
	Sugar, Powder	654.79	13.0958	13.105

	Talc	27.68	0.5536	0.5546
	Light Mineral Oil	15.08	0.3016	0.3081
I	Calcium Carbonate	500.00	10.0000	10.009
	Starch(Corn)	71.43	1.4286	1.4251
	Sugar, Powder	654.79	13.0958	13.08
	Talc	27.68	0.5536	0.5591
	Light Mineral Oil	15.08	0.3016	0.3051
	Sod.Hexa Metaphosphate	4.55	0.091	0.0938

Results:

Rossett & Rice Tests

Figure 11 demonstrates a study comparing the effect of the processed vs. unprocessed material. The blends are similar in composition, but differ in method of formation, i.e. Granulated vs. dry blend.

Unprocessed/Dry Blend: Formula 1 + Starch

Processed/Granulated Blend: Formula 2 + $CaCO_3$ with Starch

Figure 12 demonstrates a study comparing the effect of processed vs. unprocessed material. The blends are similar in composition, but differ in method of formation, i.e. Granulated vs. dry blend.

Unprocessed/Dry Blend: Formula 1 + Sugar

Processed/Granulated Blend: Formula 2 +$CaCO_3$ with Sugar

Figure 13 demonstrates a study comparing the effect of processed vs. unprocessed material. The blends are similar in composition, but differ in method of formation, i.e. Granulated vs. dry blend.

Unprocessed/Dry Blend: Formula 1 + Talc

Processed/Granulated Blend: Formula 2 +$CaCO_3$ with Talc

Figure 14 demonstrates a study comparing the effect of processed vs. unprocessed material. The blends are similar in composition, but differ in method of formation, i.e. Granulated vs. dry blend.

Unprocessed/Dry Blend: Formula 1 + NaHMP

Processed/Granulated Blend: Formula 2 +$CaCO_3$ with NaHMP

Figure 15 demonstrate a study comparing the effect of processed vs. unprocessed material. The blends are similar in composition, but differ in method of formation, i.e. Granulated vs. dry blend.

Unprocessed/Dry Blend: Formula 1 + Starch + Sugar

Processed/Granulated Blend: Formula 2 + $CaCO_3$ with Starch and Sugar)

Figure 16 demonstrates a study comparing the effect of processed vs. unprocessed material. The blends are similar in composition, but differ in method of formation, i.e. Granulated vs. dry blend.

Unprocessed/Dry Blend: Formula 1 + Starch + Sugar+ Talc

Processed/Granulated Blend: Formula 2 + CaCO3 with Starch, Sugar and Talc

Figure 17 demonstrates a study comparing the effect of processed vs. unprocessed material. The blends are similar in composition, but differ in method of formation, i.e. Granulated vs. dry blend.

Unprocessed/Dry Blend: Formula 1 + Starch + Sugar+Talc+LMO+NaHMP

Processed/Granulated Blend: Formula 2 + CaCO3 with Starch, Sugar, Talc, LMO, and NaHMP

Analysis of Rossett & Rice Tests

Table 6 shown below demonstrates the analysis of the Blends as described above.

Sample ID	Last Reading in minutes (Last pH)
Dry Blend: A	
Run One	108 (1.05)
Run Two	102 (2.15)
Granulated Blend: A	
Run One	234 (4.96)
Run Two	176 (2.97)
Dry Blend: B	
Run Two	82 (2.89)
Run Three	92 (2.88)
Granulated Blend: B	
Run One	208 (3.46)
Run Two	204 (6.11)
Dry Blend: C	
Run One	88 (1.78)
Run Two	138 (2.74)
Granulated Blend: C	
Run One	150(2.85)
Run Two	182 (4.39)
Dry Blend: D	
Run One	44 (2.11)
Run Two	122 (3.04)
Granulated Blend: D	
Run One	172 (5.34)
Run Two	180 (3.03)
Dry Blend: E	
Run One	122 (2.92)
Run Two	98 (2.43)
Granulated Blend: E	
Run One	180 (5.41)
Run Two	178 (5.45)

Dry Blend: F	
Run One	184 (3.03)
Run Two	200 (3.33)
Granulated Blend: F	
Run One	188 (2.91)
Run Two	206 (2.99)
Dry Blend: G	
Run One	172 (1.33)
Run Two	152 (2.40)
Granulated Blend: G	
Run One	200 (4.24)
Run Two	200 (6.19)
Dry Blend: H	
Run One	104 (1.86)
Run Two	132 (2.86)
Granulated Blend: H	
Run One	172 (2.98)
Run Two	176 (5.85)
Dry Blend: I	
Run One	126 (3.01)
Run Two	180 (2.88)
Granulated Blend: I	
Run One	218 (2.89)
Run Two	258 (5.16)

Texture Analyzer

The Table below provides the Texture Analyzer results of raft strength measured in grams, See reference blends below.

Reference Blends

Unprocessed Blends/Dry Blends:

A. Formula 1 + Starch
B. Formula 1 + Sugar
C. Formula 1 + Talc
D. Formula 1 + Light mineral oil
E. Formula 1 + Sodium Hexametaphosphate.
F. Formula 1 + Starch and Sugar
G. Formula 1 + Starch and Sugar and Talc
H. Formula 1 + Starch and Sugar and Talc and LMO
I. Formula 1 + Starch, Sugar, Talc, LMO, Sodium HMP

Processed Blends/ Granulated Blends: (formula 2 is the formation of a dry blend without CaCO3 as described above

A. Calcium Carbonate (500 mg) + Starch (granulate and dry) and Formula 2
B. Calcium Carbonate (500 mg) + Sugar (granulate and dry) and Formula 2
C. Calcium Carbonate (500 mg) + Talc (granulate and dry) and Formula 2
D. Calcium Carbonate (500 mg) + LMO (granulate and dry) and Formula 2
E. Calcium Carbonate (500 mg) + Sodium HMP (granulate and dry) and Formula 2
F. Calcium Carbonate (500 mg) + Starch and Sugar (granulate and dry) and Formula 2
G. Calcium Carbonate (500 mg) + Starch, Sugar ,Talc (granulate and dry) and Formula 2
H. Calcium Carbonate (500 mg) + Starch, Sugar, Talc, LMO (granulate and dry) and Formula 2
I. Calcium Carbonate (500 mg) + Starch, Sugar, Talc, LMO, Sodium HMP (granulate and dry) and Formula 2

Table 7

Average forces of the Texture Analyzer Tests

Sample Blend	Average force in grams
A: Dry Blend	4.271
A: Granulated Blend	5.402
B: Dry Blend	4.654
B: Granulated Blend	7.354
C: Dry Blend	5.709
C: Granulated Blend	5.114
D: Dry Blend	5.172
D: Granulated Blend	4.047
E: Dry Blend	5.038
E: Granulated Blend	5.367
F: Dry Blend	5.435
F: Granulated Blend	5.788
G: Dry Blend	6.488
G: Granulated Blend	7.43
H: Dry Blend	5.767
H: Granulated Blend	9.015
I: Dry Blend	4.893
I: Granulated Blend	11.016

Rossett & Rice Tests

The five excipients starch, sugar, talc, light mineral oil, and sodium hexametaphosphate were each tested in various blends for their effect on raft formation when processed or not processed. The results are as follows:

Blends with Starch

a. Unprocessed/Dry Blend: Both run one and run two depict a weak raft that lasts for approximately 100 minutes.

b. Processed/Granulated Blend: Although there is over an hour discrepancy between the two runs, it is evident that processing has a significant effect on the raft with starch.

Blends with Sugar

a. Unprocessed/Dry Blend: Both runs one and two last for less than 100 minutes, the raft is weak.

b. Processed/Granulated Blend: Both runs demonstrate the ability of granulated sugar with a blend to last for at least 200 minutes, a dramatic improvement from previous runs with sugar.

Blends with Talc

a. Unprocessed/Dry Blend: There is a large 40 minute discrepancy between the two runs so it is difficult to evaluate the raft

b. Processed/Granulated Blend: Owing to the inconsistency of the dry blends, it is difficult to conclude that processing does/does not have an effect on talc.

Blends with LMO

a. Unprocessed/Dry Blend: The raft is most probably unstable, therefore results of two runs differ by over an hour.

b. Processed/Granulated Blend: Results from first two runs of unprocessed material are very varied, but most likely processing has no effect on LMO.

Blends with NaHMP

a. Unprocessed/Dry Blend: Run two lasts for only 24 minutes longer than the first, so the results are consistent. Also, the runs terminate at 98 minutes and 122 minutes, therefore the raft is relatively stronger than blends with other excipients.

b. Processed/Granulated Blend: The consistency and durability of the unprocessed blends are surpassed by the results of the processed blends, therefore it can be concluded that granulation has an effect on sodium hexametaphosphate.

Blends with Starch and Sugar

a. Unprocessed/Dry Blend: The combination of starch and sugar alone has a strong effect on the raft neutralization activity.

b. Processed/Granulated Blend: Although processing does not have an effect on the combination of these two excipients, the durability of the raft is clearly controlled by the composition of the raft rather than the formation of it.

Blends with Starch, Sugar and Talc

a. Unprocessed/Dry Blend: Without processing, one can conclude that the combination of these three excipients has a strong impact on raft neutralization activity

b. Processed/Granulated Blend: Although it is difficult to see in the graph, processing does have a slight impact on the excipient combination. Even after 200 minutes the pH is still relatively neutral.

Blends with Sugar, Starch, Talc and LMO

a. Unprocessed/Dry Blend: Without processing, the combination of these four excipients forms a raft weaker than expected. By evaluating the previous graphs of combinations of excipients, one would expect Figure 10 to have longer lasting Dry Blend graphs.

b. Processed/Granulated Blend: In the graph with the four excipients, it is apparent that processing improved the raft neutralization activity

Blends with Starch, Sugar, Talc, LMO, and NaHMP

a. Unprocessed/Dry Blend: The unprocessed material lasts for a very long time, indicating that the combination of excipients is effective

b. Processed/Granulated Blend: Although the two runs are slightly different, it is evident that processing had an impact on the excipients. This can be concluded because both runs ran well over 200 minutes.

Texture Analyzer

The texture analyzer is designed to measure the strength of the raft. It is important for the raft to have a high penetration force to be able to protect against acid reflux. In the results, as seen in above, processed blends were consistently resulting in higher penetration forces than dry blends. The only exceptions were LMO and Talc because of their poor solubility in water (solubility in water is essential because of the nature of the granulation process). Therefore, it can be concluded that processing has a greater effect on raft strength than without processing.

When analyzing the excipients as individual blends, the results show that sugar alone, once processed, provides one of the strongest rafts. However, once the ingredients of the MB are combined, all five excipients, starch, sugar, talc, light mineral oil, and sodium hexametaphosphate, when combined produce the strongest raft formed.

Thus this experiment demonstrates the blends processed by way of a granulation are more likely to result in longer lasting and stronger raft formations than an unprocessed blend.

EXPERIMENT 5

The following tables demonstrate using the methodologies described herein, more fully the differences in raft strength between a non-compressible calcium (Table 8), a granulate, processed blend (Table 9), and a granulated, processed blend which has both a sweetener and a binding agent granulated together (Table 10).

For the on processed calcium carbonate powder, the brand name "Albagloss" made by a company called Specialty Minerals was used. This material is 100% pure calcium carbonate and is not a granulation.

For the experiments of Table 8, the unprocessed blends, the excipients have been mixed as listed in the Table which the R&R and Texture Analysis conducted thereon. The experiments with the unprocessed blends did not involve any granulation or tabletting.

In case of the processed blends (i.e., granulated blends) the following preparation steps were taken. The calcium carbonate used in these blends is same as the one used in the unprocessed blends (Albagloss). A double amount (two tablets dose equivalent) of $CaCO_3$ and other excipients shown in the table were weighed out and mixed and ground together in a coffee grinder, except alginic acid, $KHCO_3$ and mannitol. A suitable amount of water was added to form good granules. The granules were then dried in an oven and milled using mortar and pestle to obtain desired particle size. The granules were then blended with alginic acid, potassium bicarbonate and mannitol, and the resulting final blend was used in R&R and Texture analysis testing.

The mixture is transferred to a jacketed 250 ml. Beaker. To the beaker was added 20 ml. of 37^{O} C water and mixed well until dispersed completely. To this is added 100 ml. of 37^{O} C 0.1N HCl to form a raft. A magnetic stirrer is added to the jacketed 250 ml. beaker and started to rotate at speed of 100 rpm. To this is inserted two rubber tubes into the testing beaker, into which is pumped at 37^{O} C 0.1N HCl solution and pump out 37^{O} C 0.1N HCl solution at the speed of 2 ml/minute concurrently. One pH probe is inserted to measure the pH of solution below the raft and another pH probe inserted to measure pH of the raft. The

pH is measured at 2 minutes interval and both pH measurements are recorded. An average length of two tests in minutes to reach pH 4.0 is tabulated in the tables shown below.

In Table 10, reference is made to the MB formulation, which is described earlier.

TABLE 8

Raft Data

Simple Unprocessed Physical Blend									Raft	R&R test
$CaCO_3$ 500 mg	Alginic acid 200 mg	$KHCO_3$ 140 mg	Mannitol 800 mg	Starch 71.43 mg	Sugar 654.8 mg	Talc 27.68 mg	LMO 15.08 mg	NaHMP 4.55 mg	Strength Force in gram	Raft in min. to reach to pH 4.0
$CaCO_3$	Alg-acid	$KHCO_3$							4.505	12
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol						6.077	31
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol	Starch					4.271	97
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol		Sugar				4.654	73
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol			Talc			5.709	93
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol				LMO		5.172	80
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol					NaHMP	5.038	106
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol	Starch	Sugar				5.435	163
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol	Starch	Sugar	Talc			6.488	157
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol	Starch	Sugar	Talc	LMO		5.767	100
$CaCO_3$	Alg-acid	$KHCO_3$	Mannitol	Starch	Sugar	Talc	LMO	NaHMP	4.893	131

TABLE 9

Simple Blend (Processed)									Raft	R&R test
CaCO3 500 mg	Alginic acid 200 mg	KHCO3 140 mg	Mannitol 800 mg	Starch 71.43 mg	Sugar 654.8 mg	Talc 27.68 mg	LMO 15.08 mg	NaHMP 4.55 mg	Strength Force in gram	Raft in min. to reach to pH 4.0
CaCO3*	Alg-acid	KHCO3							6.510	55
CaCO3*	Alg-acid	KHCO3	Mannitol						6.549	56
CaCO3**	Alg-acid	KHCO3	Mannitol	Starch					5.402	198
CaCO3**	Alg-acid	KHCO3	Mannitol		Sugar				7.354	200
CaCO3**	Alg-acid	KHCO3	Mannitol			Talc			5.114	163
CaCO3**	Alg-acid	KHCO3	Mannitol				LMO		4.047	163
CaCO3**	Alg-acid	KHCO3	Mannitol					NaHMP	5.367	179
CaCO3**	Alg-acid	KHCO3	Mannitol	Starch	Sugar				5.788	179
CaCO3**	Alg-acid	KHCO3	Mannitol	Starch	Sugar	Talc			7.430	205
CaCO3**	Alg-acid	KHCO3	Mannitol	Starch	Sugar	Talc	LMO		9.015	162
CaCO3**	Alg-acid	KHCO3	Mannitol	Starch	Sugar	Talc	LMO	NaHMP	11.016	225

CaCO3* : granulated with water.
CaCO3** : granulated with starch, sugar, talc, LMO(liquid mineral oil) and NaHMP(sodium hexametaphosphate).

TABLE 10

MB with various sugars								Raft	R&R test
MB 1293.6 mg	Alginic acid 200 mg	$KHCO_3$ 140 mg	Mannitol 800 mg	Sorbitol 800 mg	Xylitol 800 mg	Dextrose 800 mg	Fructose 800 mg	Strength Force in gram	Raft in min. to reach to pH 4.0
MB	Alg-acid	KHCO3	Mannitol					16.042	230
MB	Alg-acid	KHCO3		Sorbitol				13.912	228
MB	Alg-acid	KHCO3			Xylitol			16.777	244
MB	Alg-acid	KHCO3				Dextrose		15.966	218
MB	Alg-acid	KHCO3					Fructose	19.728	249

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the are can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples herein are to be construed as merely illustrative and not a limitation of the
scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A pharmaceutical composition for a chewable tablet comprising alginic acid or a salt thereof, at least one water soluble carbonate radical precursor, at least one calcium salt, and at least one of a first bulk sweetener, or a binding agent wherein the calcium salt, and bulk sweetener or binding agent prior to admixture with the alginic acid and carbonate precursor, are combined together by a wet granulation process, and wherein the composition may optionally further comprise at least one of a second bulk sweetener, talc, mineral oil, and an alkali metal salt of hexametaphosphate, a flavouring agent, an intense sweetener, or a dye.

2. The chewable tablet according to claim 1, in which said alginic acid is present in an amount from about 70 to about 500 mg per tablet.

3. The chewable tablet according to claim 2, in which said alginic acid is present in an amount from about 200 to about 400 mg per tablet.

4. The chewable tablet according to claim 3, in which said alginic acid is present in an amount from about 140 to about 300 mg per tablet.

5. The chewable tablet according to claim 1, in which said carbonate radical precursor is a carbonate or bicarbonate of an alkali or alkaline earth metal.

6. The chewable tablet according to claim 5, in which said metal is sodium, potassium, calcium, magnesium or manganese.

7. The chewable tablet according to claim 6 in which the carbonate radical precursor is potassium bicarbonate or sodium bicarbonate or a mixture thereof.

8. The chewable tablet according to claim 7 in which the potassium bicarbonate or sodium bicarbonate or a mixture thereof is present in an amount from about 50 to about 200 mg per tablet.

9. The chewable tablet according to claim 8 in which the potassium bicarbonate or sodium bicarbonate or a mixture thereof is present in an amount from about 70 to about 160 mg per tablet.

10. The chewable tablet according to claim 1 in which the calcium salt is calcium citrate, calcium maleate, calcium citrate maleate, calcium carbonate, calcium lactate, calcium glyceryl phosphate, or calcium phosphate.

11. The chewable tablet according to claim 10 in which the calcium salt is calcium carbonate.

12. The chewable tablet according to claim 1 in which the calcium salt is present in an amount from about 100 to about 1000 mg free calcium per tablet.

13. The chewable tablet according to claim 12 in which the calcium salt is present in an amount from about 250 to about 1000 mg per tablet.

14. The chewable tablet according to claim 10 in which the calcium salt is present in an amount of about 500 mg per tablet.

15. The chewable tablet according to claim 1, wherein binding agent is a starch, a natural gum, a low viscosity cellulosic derivative.

16. The chewable tablet according to claim 15 wherein the binding agent is a starch which is corn starch, modified corn starch, wheat starch, modified wheat starch, Starch 1500, or pregelatinized starch.

17. The chewable tablet according to claim 16 wherein the starch is corn starch or modified corn starch.

18. The chewable tablet according to claim 15 or 16 wherein the starch is present in an amount from about 1 % to about 15% of the tablet weight.

19. The chewable tablet according to claim 15 wherein the binding agent is a low viscosity cellulosic derivative which is carbomer, HPMC, MC, HPC, MCC, CMC, HEC, or methylcellulose.

20. The chewable tablet according to claim 19 wherein the cellulosic is present in an amount from about 1 % to about 10% of the tablet weight.

21. The chewable tablet according to claim 15 wherein the binding agent is a natural gum which is gum arabic, accacia, carrageenan, guar or tragacanth.

22. The chewable tablet according to claim 21 wherein the natural gum is present in an amount from about 0.5% to about 7% of the tablet weight.

23. The chewable tablet according to claim 1 wherein the binding agent is povidone, maltodextrin, mannitol, sorbital, polaxomer, polydextrose, PEG, or a polymethacrylate.

24. The chewable tablet according to claim 1 wherein the first bulk sweetener is a sugar which is dextrose, sucrose, lactose, confectionery sugar, powdered sugar, dextrin, fructose, glucose, polydextrose, sorbitol, malititol, maltose, mannitol, xylitol, or a combination thereof.

25. The chewable tablet according to claim 21 wherein the first bulk sweetener is a sugar which is dextrose or sucrose or a combination thereof.

26. The chewable tablet according to claim 1 wherein the first bulk sweetener is a polyol which is mannitol, sorbitol, xylitol, maltitol, maltose, polydextrose, or a combination thereof.

27. The chewable tablet according to claim 23 wherein the polyol is mannitol or sorbitol or a combination thereof.

28. The chewable tablet according to claim 1 in which the first bulk sweetener which is wet granulated with the calcium salt is present in an amount from about 10 % to about 30% of the tablet weight.

29. The chewable tablet according to claim 25 in which the first bulk sweetener is a sugar which is wet granulated with the calcium salt is present in an amount from about 15% to about 25% of the tablet weight.

30. The chewable tablet according to claim 1 wherein the first bulk sweetener is a sugar which is dextrose, sucrose, lactose, confectionery sugar, powdered sugar, a polyol which is mannitol, sorbitol, xylitol, maltitol, maltose and polydextrose, or a combination thereof.

31. The chewable tablet according to claim 1 wherein the chewable tablet comprises the second bulk sweetener which is a sugar which is dextrose, sucrose, lactose, confectionery sugar, powdered sugar, or a polyol which is mannitol, sorbitol, xylitol, maltitol, maltose and polydextrose, or a combination thereof.

32. The chewable tablet according to claim 28 wherein the second bulk sweetener is a sugar which is dextrose, sucrose, lactose, confectionery sugar, powdered sugar, or a combination thereof.

33. The chewable tablet according to claim 28 wherein the second bulk sweetener is a polyol which is mannitol, sorbitol, xylitol, maltitol, maltose and polydextrose, or a combination thereof.

34. The chewable tablet according to claim 30 wherein the second bulk sweetener is a polyol which is mannitol, or sorbitol or a combination thereof.

35. The chewable tablet according to claim 28 wherein the second bulk sweetener is or is a polyol which is mannitol, or sorbitol in combination with dextrose.

36. The chewable tablet according to claim 28 or 31 wherein the second bulk sweetener is present in an amount from about 200mg to about 1000mg per tablet or . 8% to 40% % by weight of the tablets.

37. The chewable tablet according to claim 1 wherein the first bulk sweetener and the second bulk sweetener are not the same.

38. The chewable tablet according to claim 1 wherein the first bulk sweetener is sucrose, mannitol or dextrose and the second bulk sweetener is mannitol, sorbitol or dextrose.

39. The chewable tablet according to claim 1 wherein the binding agent and the first bulk sweetener are blended together with the calcium salt by wet granulation.

40. The chewable tablet according to claim 36 wherein the binding agent is present in an amount from about 1% to about 15%; and the first bulk sweetener is present in an amount from about 10% to about 30% and the calcium salt is present in an amount from about 10% to about 50% by weight of tablet.

41. The chewable tablet according to claim 37 wherein the binding agent is corn starch, the first bulk sweetener is sucrose, and the calcium salt is calcium carbonate.

42. The chewable tablet according to claim 1 wherein the talc is present in an amount from about 0.5% to about 3% of the tablet weight.

43. The chewable tablet according to claim 1 wherein the intense sweetener is acesulfame-K, saccharin, aspartame, sucralose, or a combination thereof.

44. The chewable tablet according to claim 1 wherein the intense sweetener is present in an amount from about 0.02% to about 0.12% of the tablet weight.

45. The chewable tablet according to claim 1 wherein the mineral oil is present in an amount from 0% to about 1% of the tablet weight.

46. A method of calcium supplementation by administering to a mammal in need thereof, an effective amount of a composition according to any one of claims 1 to 45.

47. A method of reducing gastric reflux in a human in need thereof, comprising administering to said human an effective amount of a composition according to any one of claims 1 to 45.

48. A method of reducing heartburn in a human in need thereof, comprising administering to said human an effective amount of a composition according to any one of claims 1 to 45.

49. A method of reducing the incidence of gastric reflux in the esophageal cavity in a human for a period of time, post ingestion of a meal sufficient to cause gastric reflux in said human for a time period of about 60 to about 480 minutes comprising administering to said human an effective amount of a composition according to any one of claims 1 to 45.

50. The method according to claim 49 wherein the time period is from about 120 to about 300 minutes.

51. A method of maintaining a pH of about 4.0 or higher in the esophageal cavity of a human in need thereof, for a time period from about 60 to about 480 minutes comprising administering to said human an effective amount of a composition according to any one of claims 1 to 45.

52. The method according to claim 51 wherein the pH is 5.0 or higher.

53. The method according to claim 51 wherein the time period is from about 120 to about 300 minutes.

54. The method according to claim 48 wherein the time period is about 120 to 180 minutes.

55. A pharmaceutical composition comprising calcium carbonate, sugar, mannitol, corn starch, alginic acid and potassium bicarbonate or sodium bicarbonate in the form of a chewable tablet.

56. The composition according to claim 55 wherein the alginic acid is present in an amount of about 8%; potassium bicarbonate is present in an amount of about 6%; calcium carbonate in present in an of about 20% w/w; starch is present in amount about 5 %; sugar is present in an amount about 26%; and mannitol is present in an amount of about 32% by weight of the tablet.

57. The composition according to claim 56 which further comprises an intense sweetner present in an amount of about .1 %; and talc is present in an amount about 1%.; light mineral oil present in an amount about .6%; sodium hexametaphosphate is present in an amount about .2%; and calcium sterate present in an amount of about .5% by weight of the tablet.

Abstract

A pharmaceutical composition for the suppression of gastric reflux comprising an alginate, potassium or sodium bicarbonate (or a mixture thereof), and a calcium salt, such as calcium carbonate which demonstrates a long lasting and highly durable raft in vivo.

Figure 1

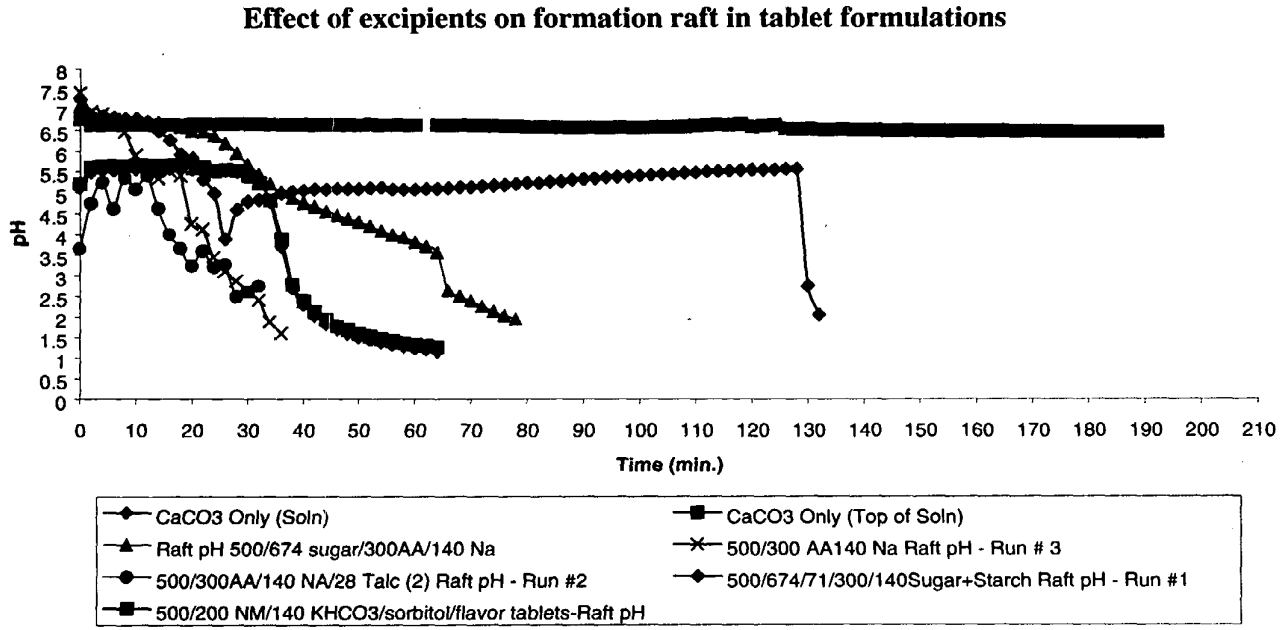

Effect of excipients on formation raft in tablet formulations
pH
Time (min.)
CaCO3 Only (Soln)
CaCO3 Only (Top of Soln)
Raft pH 500/674 sugar/300AA/140 Na
500/300 AA140 Na Raft pH - Run # 3
500/300AA/140 NA/28 Talc (2) Raft pH - Run #2
500/674/71/300/140Sugar+Starch Raft pH - Run #1
500/200 NM/140 KHCO3/sorbitol/flavor tablets-Raft pH

Figure 2. Schematic diagram of Rossett and Rice test set up.

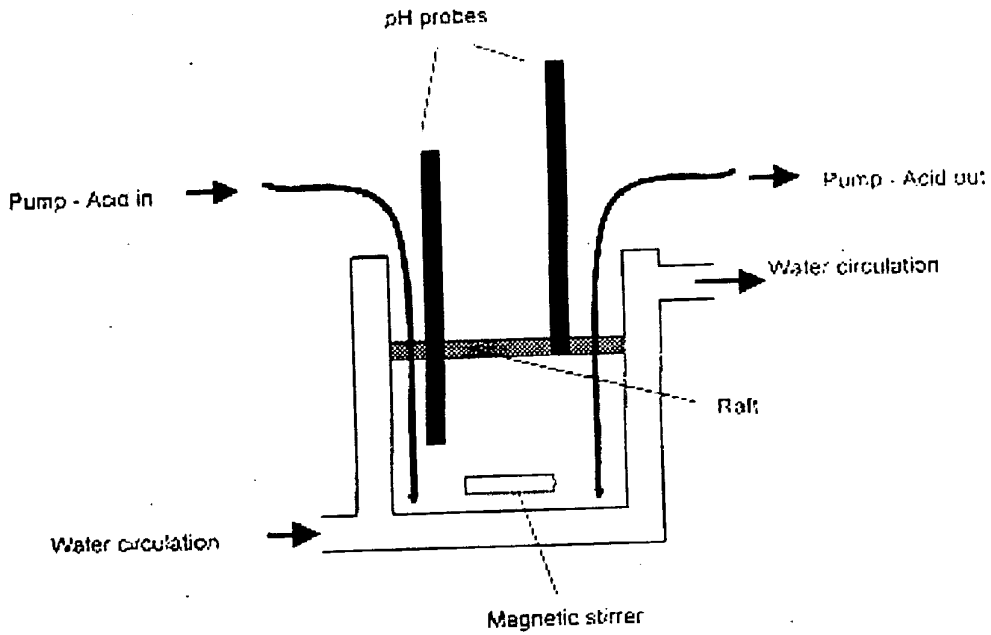


Figure 3 (Graph C)

500 mg $CaCO_3$ granulation (No Lub) + 300 mg Alginic Acid + 140 mg $KHCO_3$ using 20 ml water - Run # 1,2

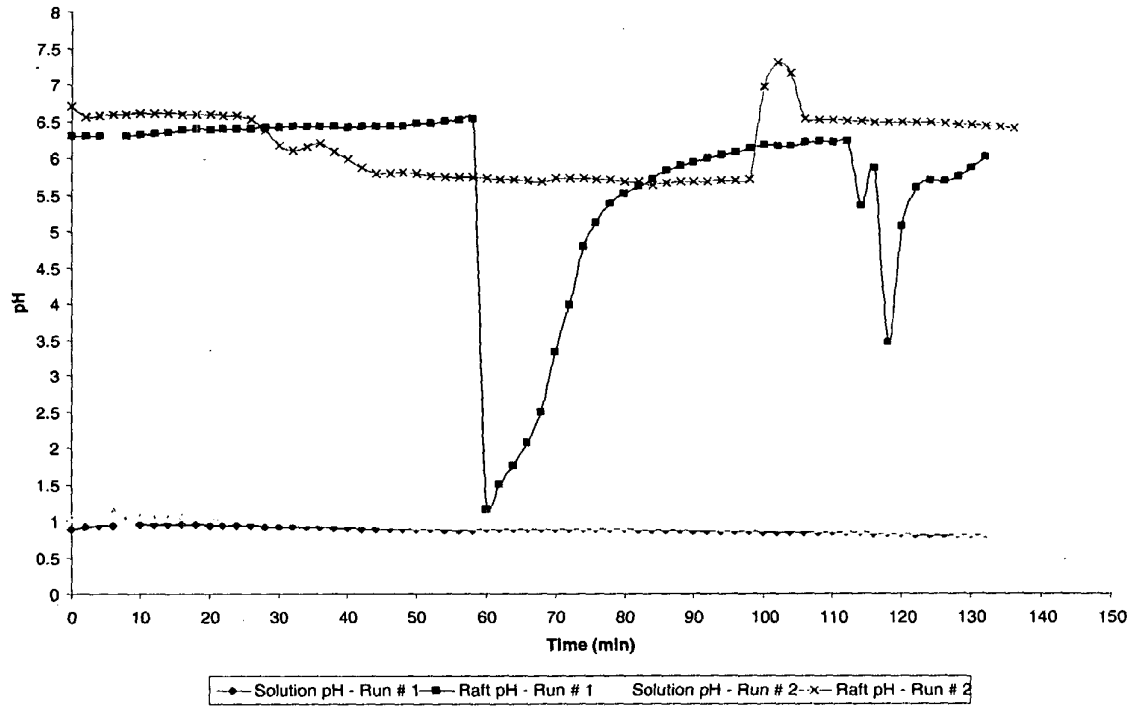


Figure 4 (Graph D)

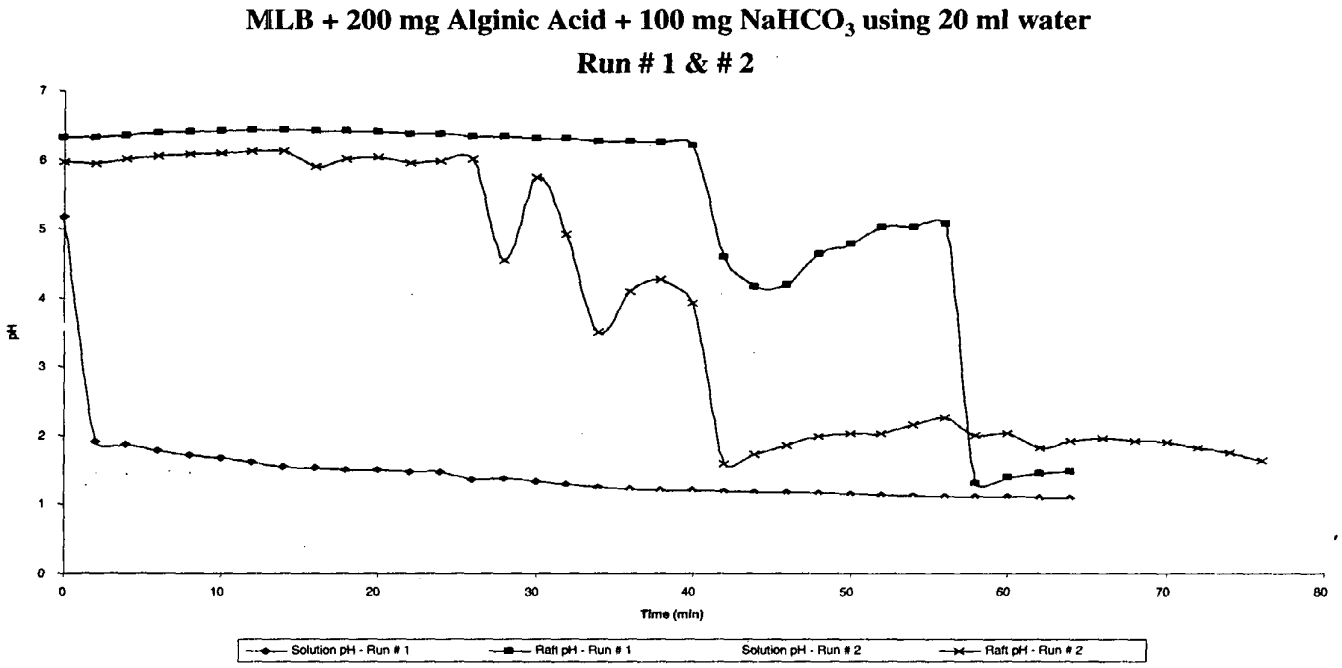


Figure 5 (Graph E)

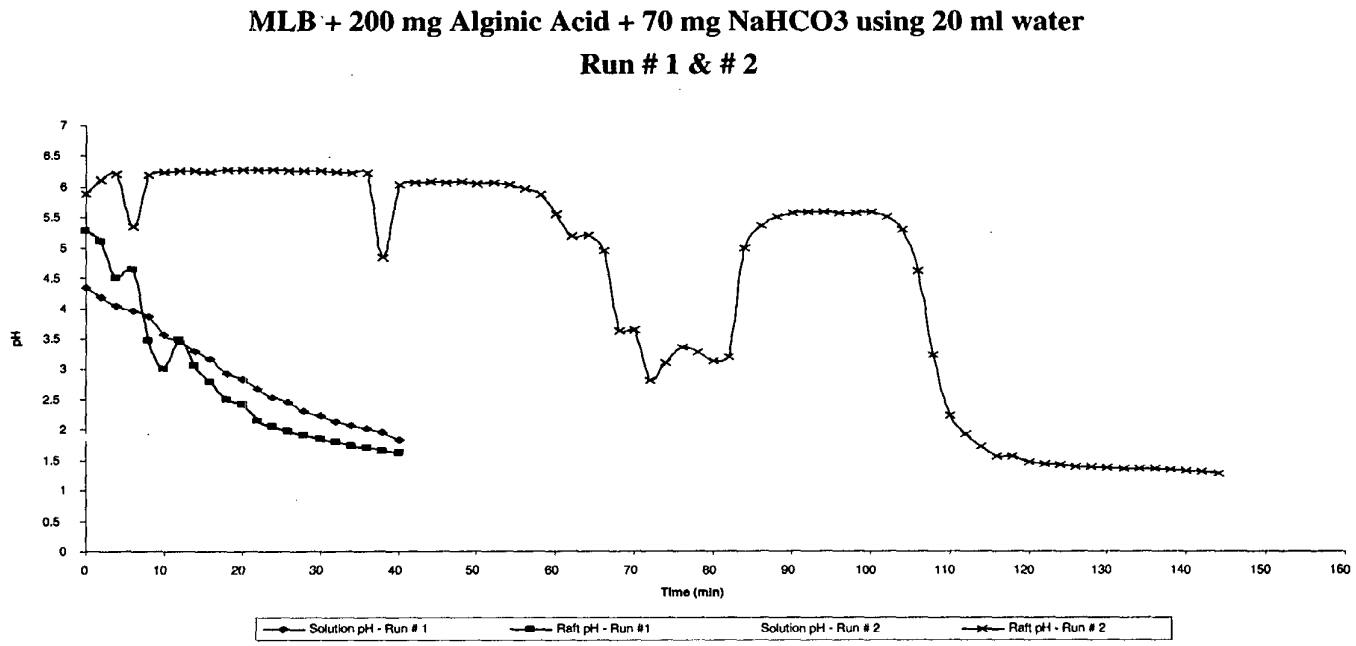


Figure 6 (Graph F)

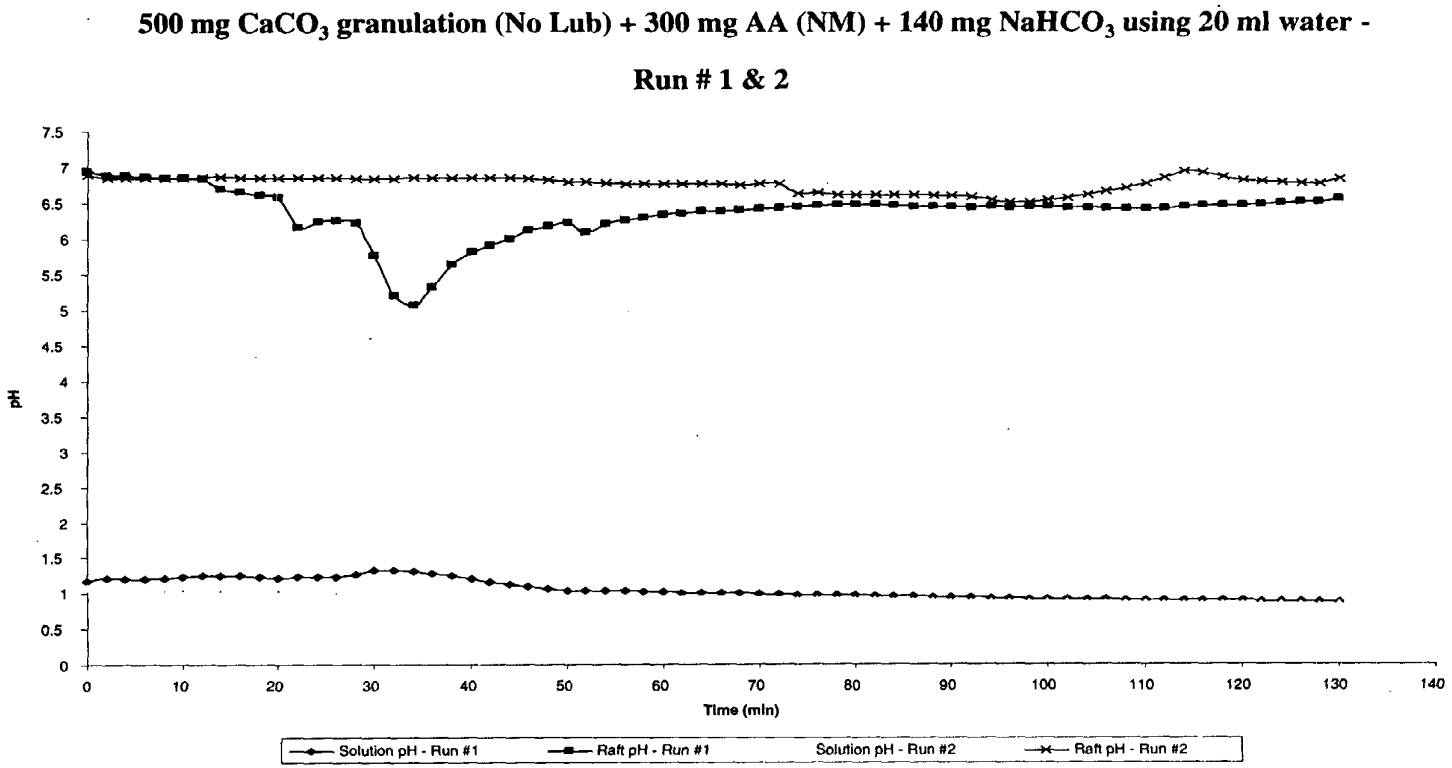


Figure 7 (Graph G)

500 mg $CaCO_3$ granulation (No Lub) +300 mg AA + 70 mg $NAHCO_3$ + 70 mg $KHCO_3$ using 20 ml water -Run # 1 & #2

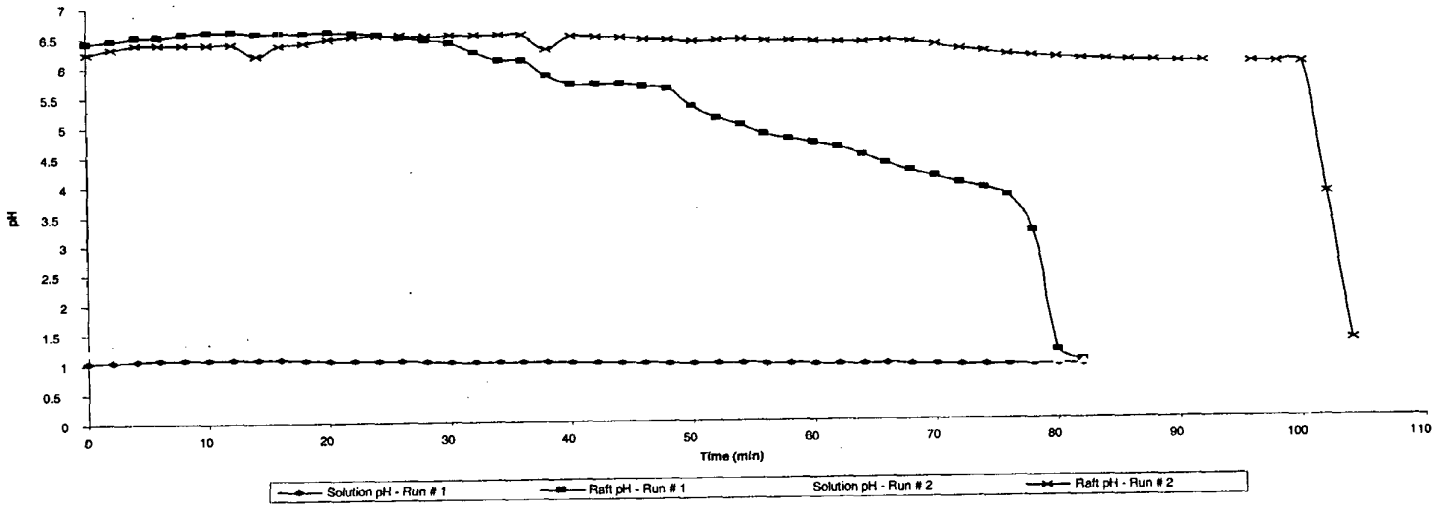


Figure 8

Master Blend + Alginic acid 400mg + Sodium Bicarbonate 140mg + Sorbitol 500 mg using 20ml water -

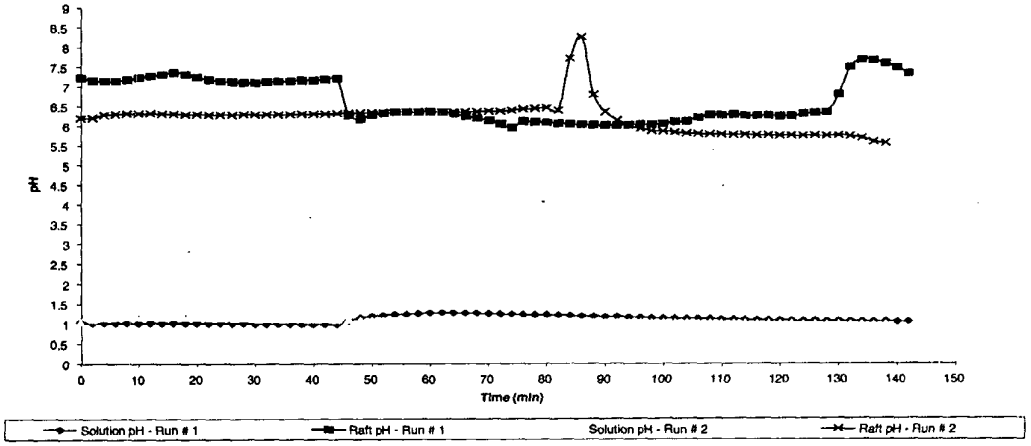


Figure 9

Master Blend + Alginic acid 400mg + Sodium Bicarbonate 140mg + Sorbitol 500 mg using 20ml water - Run # 1 & #2

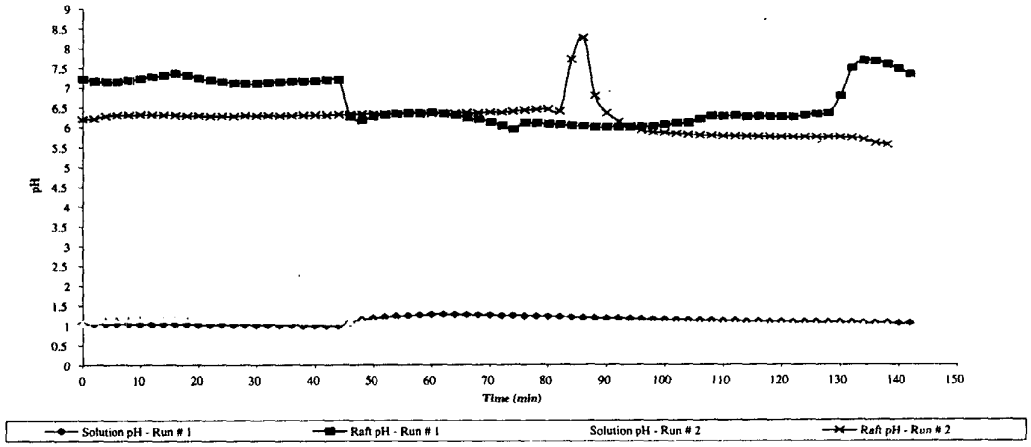


Figure 10

Master Blend + Alginic acid 400mg + Sodium Bicarbonate 140mg + Mannitol 500 mg using 20ml water

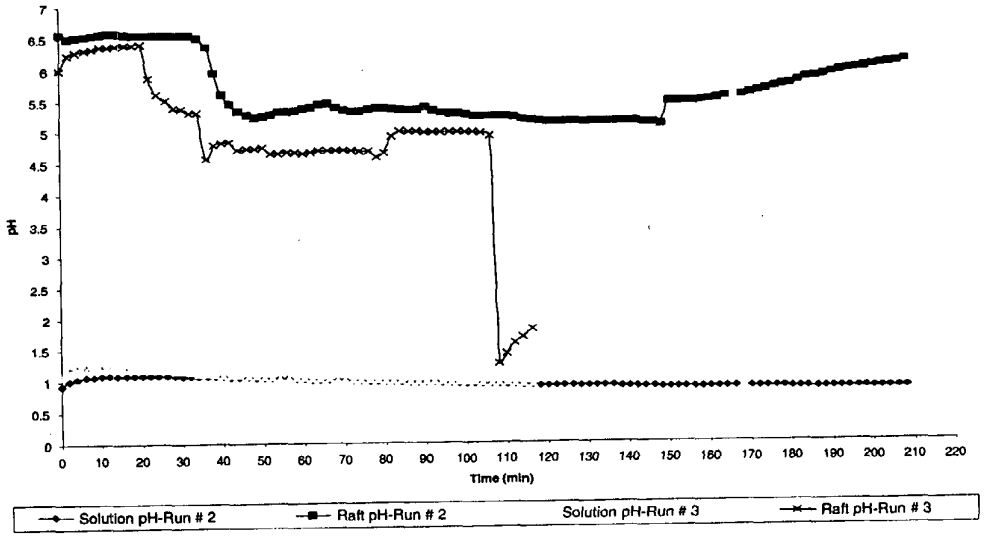


Figure 11

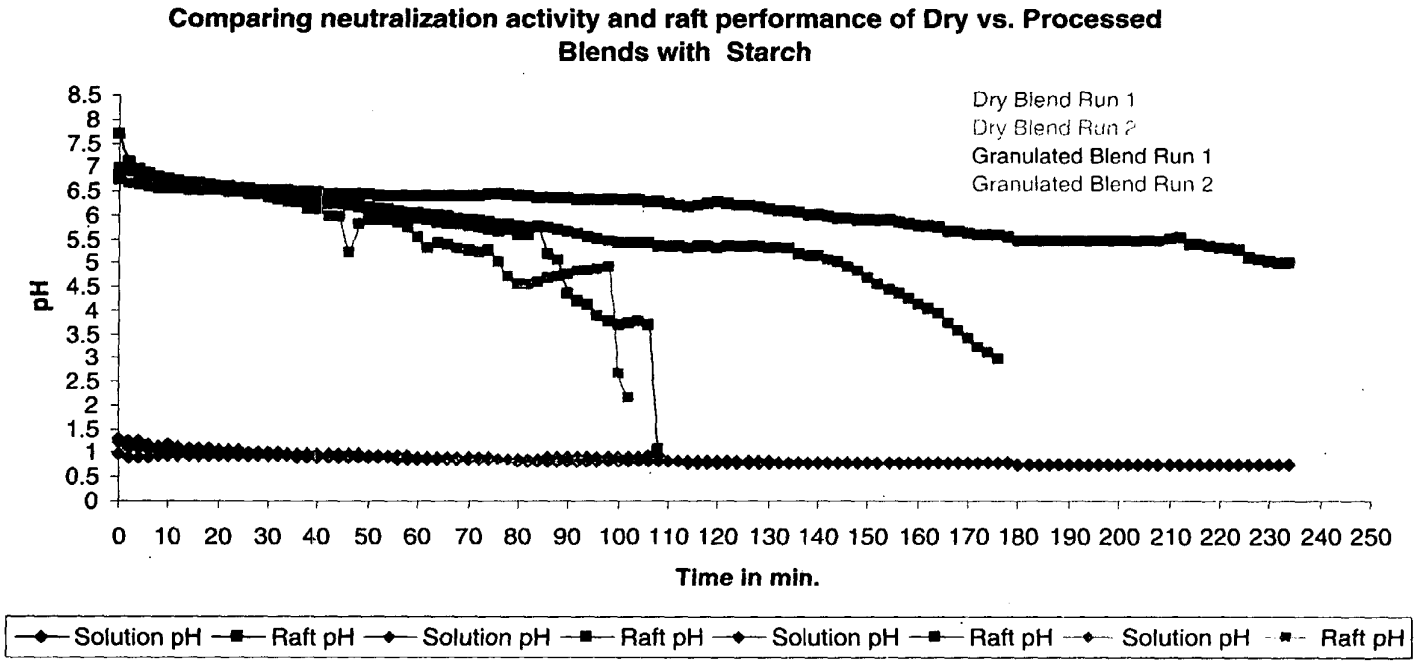

Comparing neutralization activity and raft performance of Dry vs. Processed Blends with Starch
Dry Blend Run 1
Dry Blend Run 2
Granulated Blend Run 1
Granulated Blend Run 2
pH
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250
Time in min.
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH

Figure 12

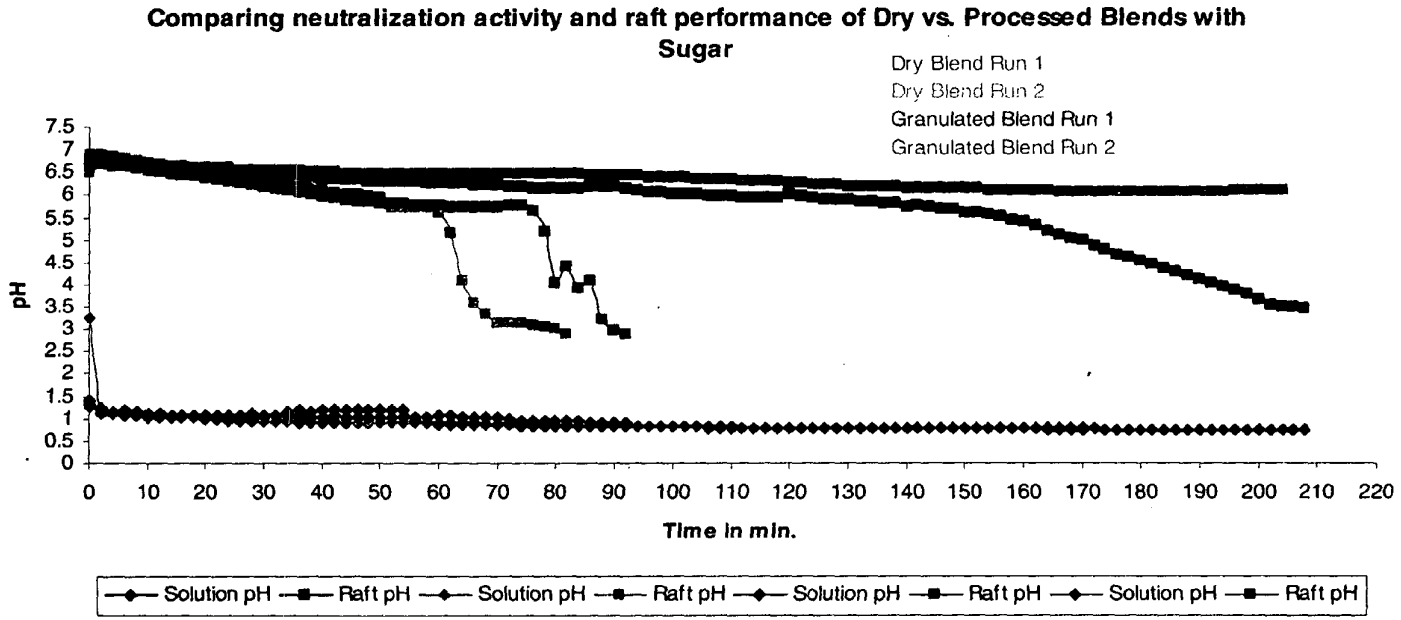

Comparing neutralization activity and raft performance of Dry vs. Processed Blends with Sugar
Dry Blend Run 1
Dry Blend Run 2
Granulated Blend Run 1
Granulated Blend Run 2
pH
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220
Time in min.
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH

Figure 13

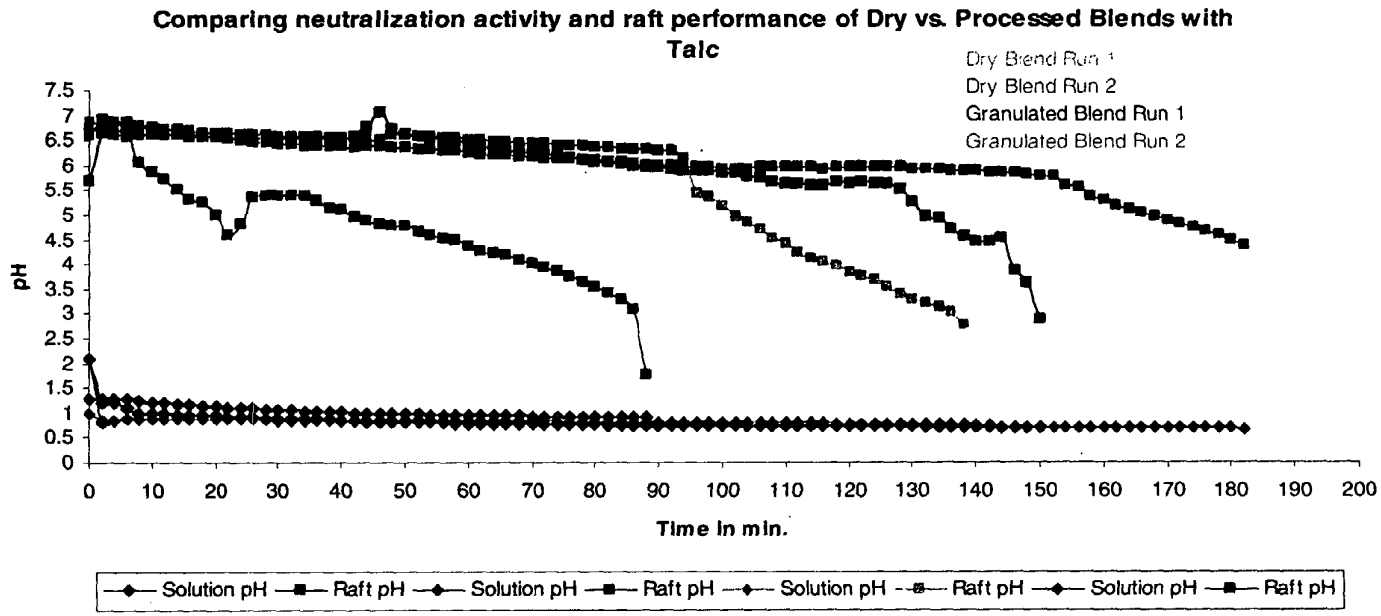

Comparing neutralization activity and raft performance of Dry vs. Processed Blends with Talc
Dry Blend Run 1
Dry Blend Run 2
Granulated Blend Run 1
Granulated Blend Run 2
pH
Time in min.
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH

Figure 14

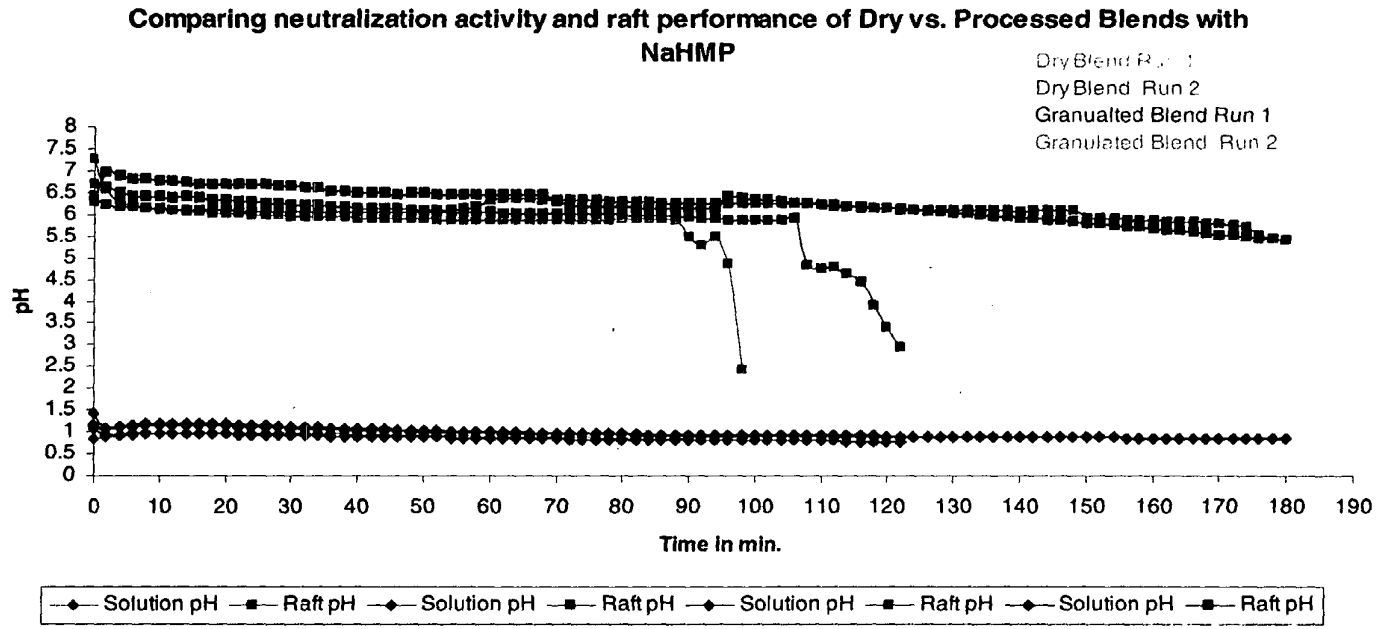

Comparing neutralization activity and raft performance of Dry vs. Processed Blends with NaHMP
Dry Blend Run 1
Dry Blend Run 2
Granualted Blend Run 1
Granulated Blend Run 2
pH
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190
Time in min.
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH

Figure 15

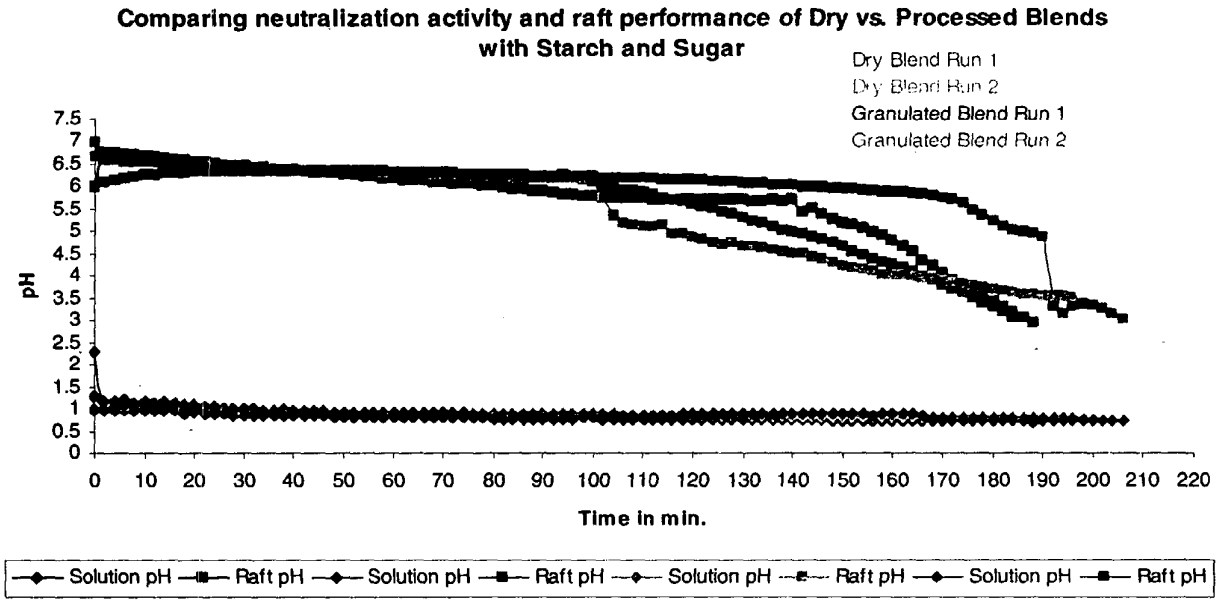

Comparing neutralization activity and raft performance of Dry vs. Processed Blends with Starch and Sugar
Dry Blend Run 1
Dry Blend Run 2
Granulated Blend Run 1
Granulated Blend Run 2
pH
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220
Time in min.
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH
Solution pH
Raft pH

Figure 16

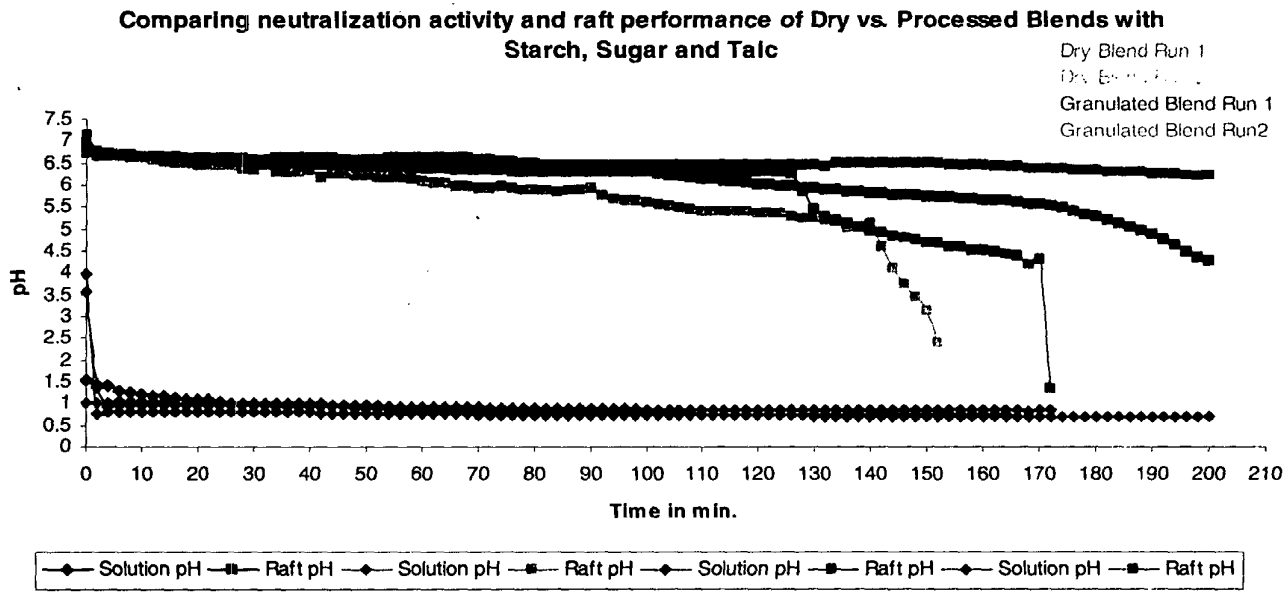
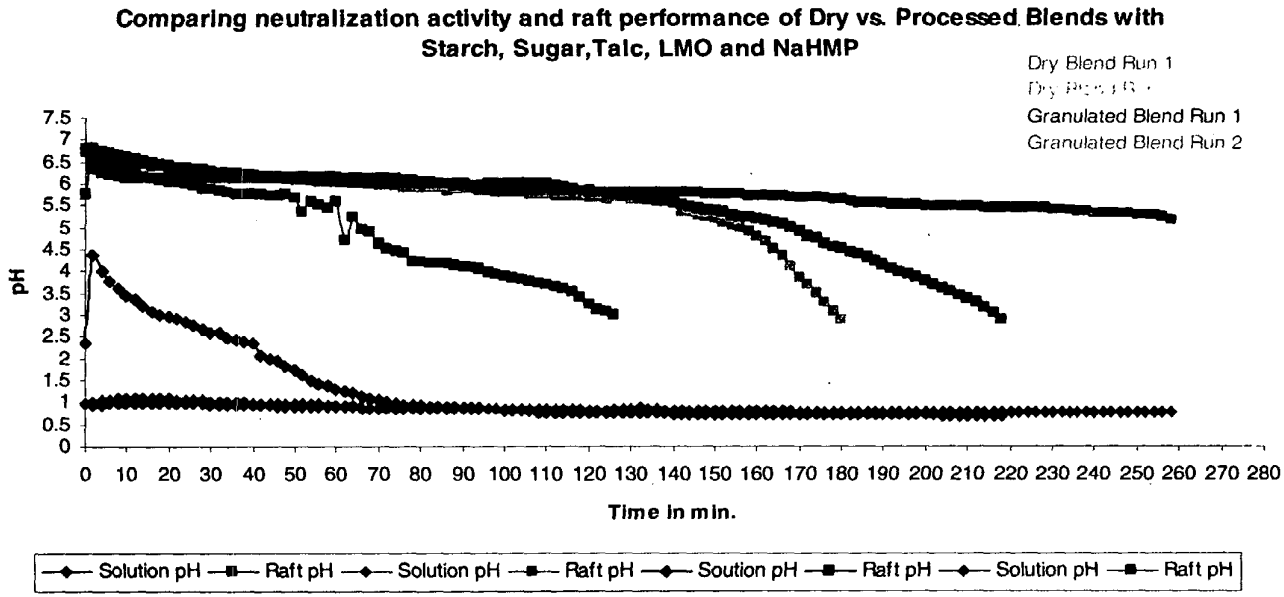

Comparing neutralization activity and raft performance of Dry vs. Processed Blends with Starch, Sugar and Talc
Dry Blend Run 1
Granulated Blend Run 1
Granulated Blend Run2
pH
Time in min.
Solution pH
Raft pH

Figure 17


Comparing neutralization activity and raft performance of Dry vs. Processed Blends with Starch, Sugar,Talc, LMO and NaHMP
Dry Blend Run 1
Granulated Blend Run 1
Granulated Blend Run 2
pH
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280
Time in min.
Solution pH
Raft pH
Solution pH
Raft pH
Soution pH
Raft pH
Solution pH
Raft pH